1027 - Diastolic Dysfunction and Heart Failure

Sunday, March 12, 2000, Noon - 2:00 p.m.
Anaheim Convention Center, Hall A
Presentation Hour: 1:00 p.m.-2:00 p.m.

1027-142 Systolic Versus Diastolic Heart Failure in Community Practice: Clinical Features and Outcomes in 1,694 Patients
Edward F. Philbin, Thomac A. Rupoo, Jr., Norman W. Linsoromth, Paul L. Jenkins. Henry Ford Hospital, Detroit, Mt. Utoy Health System, Rochester, NY, USA

Background: Patients with heart failure (HF) and abnormal versus normal left ventricular (LV) systolic function offer different in other fundamental characteristics and their clinical outcomes. This study examined such differences among patients with HF treated in community practice.

Methods: From a registry of 2,906 unsolicited consecutive patients with confirmatory HF admitted to 10 acute care community hospitals, we identiﬁed 1,694 who had measurement of LV systolic function. Charts were reviewed after hospital discharge and patients were followed prospectively for 6 months.

Results: Median age was 76 years; 56% were women. Mean ejection fraction (EF) was 36 ± 15%. A LV EF >30% of abnormal global contractility was present in 546 (50%) patients (Gys-HF), while an EF ≥ 40% or normal contractility was present in 746 (44%) (Dias-HF). Using regression analysis, older age, female sex, higher body weight, hypertensive etiology and/or ischemia were all signiﬁcant predictors of Dias-HF. Prior history of HF, diabetes, ischemic etiology, idiopathic HF and radiographic cardiomegaly also predicted Dias-HF (all P < 0.05). Mean hospital length of stay (7.4 vs 7.7 days), mean mean hospital charges (2.2 per vs 3.0) and mean NIHSS functional classes 1 month after discharge (2.2 vs 2.2) were similar between Sys-HF and Dias-HF (all P > 0.05). Crude rates of death and hospital readmission with odds ratios (OR) and conﬁdence intervals (CI) for the groups are shown in the Table. As shown, death rates were lower among Dias-HF patients while hospital readmission rates were not different.

Clinical Outcome

<table>
<thead>
<tr>
<th>In-hospital death</th>
<th>Post-discharge death</th>
<th>Total 6-month mortality</th>
</tr>
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<tbody>
<tr>
<td>Sys-HF</td>
<td>6.6%</td>
<td>15.6%</td>
</tr>
<tr>
<td>Dias-HF</td>
<td>5.1%</td>
<td>17.2%</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>0.77 (0.44-1.16)</td>
<td>0.45 (0.26-0.79)</td>
</tr>
<tr>
<td>P</td>
<td>0.17</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Conclusions: Among patients with HF hospitalized in the community setting, the sizeable subset with preserved LV systolic function has clinical characteristics and a natural history pattern different than that with abnormal LV systolic function. Thus, the assessment of LV systolic function has important diagnostic and prognostic implications in managing HF.

1027-143 From Systolic to Diastolic Chronic Heart Failure
Pierre V. Erneezat, Caroline A. Erneezat, Slaexon Miiaridowicz, Pugashendri Veyiyaraman, Edmund H. Sommarikil, Thiery H. Lejentiel, Albert Einstein College of Medicine, Bronx, New York USA

Background and methods: in order to evaluate changes in left ventricular ejection fraction (EF%) by 2D echo and functional class (FC, NYHA) in patients (pts) treated for chronic heart failure (CHF) due to systolic or diastolic dysfunction, data of 319 pts followed in our CHF clinic for an average of 32 months (range 12-73) and who at least had 2 echocardiograms over the duration of the study were analyzed.

Results: Of the 319 pts, 72 pts had an initial EF > 45%. Their EF and FC averaged 60% and 2.3 respectively, and remained unchanged during follow up. The remaining 247 pts had an initial EF < 45%. 109 pts were treated with standard therapy (SD Rx), 87 with beta blockade (BB) + SD Rx and 51 underwent coronary bypass surgery (CABG). Response to SD Rx, BB and CABG was variable: EF normalized in 90 pts while average FC did not change. In this group, FC improved by at least 1 class in 25 pts, decreased in 15 pts and remained unchanged in 50 pts.

Conclusions: Among patients with HF hospitalized in the community setting, the sizeable subset with preserved LV systolic function has clinical characteristics and a natural history pattern different than that with abnormal LV systolic function. Thus, the assessment of LV systolic function has important diagnostic and prognostic implications in managing HF.

1027-144 Is Flash Pulmonary Edema Due to Diastolic Dysfunction or Transient Systolic Dysfunction?
John Powers, Karen Fowie, Kevin Rinkin, Abdel-Mohsen Normei, Rensney Gatho, Delane Kitterman, William C. Littre. Wake Forest University School of Medicine, Winston-Salem, NC, USA

Background: Patients with flash pulmonary edema are frequently markedly hypertensive and subsequently, after control of the blood pressure (BP), found to have preserved left ventricular (LV) ejection fraction (EF). However, the pulmonary edema may not be from isolated diastolic dysfunction but instead be due to transient LV systolic dysfunction produced by hypotension and/or ischemia.

Methods: In 21 patients with flash pulmonary edema and systolic BP < 100 mmHg we evaluated LV function by 2-D echocardiography both during the acute episode and one to four days later, after treatment. There were 5 men and 16 women, age = 70 ± 11 (mean ± SD).

Results: Systolic BP during the initial echo was 200 ± 24 and was reduced to 159 ± 19 mmHg (p < 0.05) during the follow-up echo. Despite the marked difference in BP, LV EF was similar during the acute episode (0.50 ± 0.15) and after treatment (0.52 ± 0.15). EF after treatment predicted the EF during the acute episode (r = 0.88, y = 0.94x + 0.01; p < 0.05). Fourteen patients had preserved EF (>0.50) after treatment. In all those, the EF was also >0.50 during the acute episode. Similarly, the 10 patients with EF > 0.50 after treatment had EF > 0.50 during the acute episode.

Conclusions: LV ejection fraction is similar both during an acute episode of hypertensive pulmonary edema and subsequently after treatment. Thus, a preserved EF after treatment indicates that the pulmonary congestion was due to hypotensive exacerbation of diastolic dysfunction not transient systolic dysfunction.

1027-145 Evaluation of Left Ventricular Diastolic Function by the Ratio of Maximal Flow Velocity of the Early Filling Wave to its Propagation Velocity
Ehud Schawementhal, Bogdan A. Pupescu, Andrea A. Pupescu, Ello Di Segni, Elieser Kaplinsky, David Reikinovicz, Victor Guessa, Shmuel Rath, Micha S. Feinberg, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, Sackler School of Medicine, Tel Aviv University, Israel

Active left ventricular relaxation creates a small intraventricular gradient which determines the propagation velocity of the early filling wave from the base of the left ventricle to the apex (Vp), which can be assessed by color M-Mode echocardiography. Impaired relaxation will reduce Vp and cause vortex formation: as blood flow entering the ventricle interacts with stagnant blood within the cavity. In this case, maximaimal particle velocity during early filling (Vp), assessed by pulsed wave Doppler, will significantly exceed Vp. We therefore hypothesized that the ratio of Vp to Vp will be directly correlated to the severity of left ventricular pathology and examined 26 consecutive subjects: 25 normals, 20 patients with LHV and 45 patients with reduced EF. While the E/A ratio showed an expected U-shaped relation to the severity of LV pathlogy, Vp/Vp showed a direct linear correlation. Out of 24 patients with a Vp/Vp > 1.95 19 patients (79%) had either a history of pulmonary congestion or developed it within 6 months.

Conclusion: Vp/Vp is a parameter of diastolic function which increases directly with the severity of left ventricular pathology and potentially predicts outcome.


1027-146 A Rapid Bedside Test for Brain Natriuretic Peptide Accurately Delineates Both Systolic and Diastolic Dysfunction in Patients Referred for Echocardiography

Jen Koon, Judy Hope, Alex Garcia, Radmilis Kasanag, Nancy Gardetto, Anthony DeMaria, Alan S. Maisel. VAMC and UCSD, La Jolla, CA, USA

Background: As brain natriuretic peptide (BNP) accurately reflects left ventricular stretch, we hypothesized that a BNP level might be a useful diagnostic marker in screening patients for either systolic or diastolic dysfunction.

Methods: Ninety-seven subjects referred for echocardiography had BNP levels measured by a point of care immunoassay (binobline Diagnostics, La Jolla, CA). BNP results were blinded from cardiologists making the assessment of left ventricular function. Patients with normal systolic function plus E/A reversal, shortened mitral valve deceleration time and 'a' wave reversal in the pulmonary vein, were classified as diastolic dysfunction.

Results: BNP levels were significantly lower (36 ± 4 pg/ml) in normal patients than in those with either diastolic dysfunction (416 ± 31 pg/ml) or systolic dysfunction (480 ± 48 pg/ml, P < 0.001). ROC curve analysis revealed that a BNP level of 170 pg/ml predicted with 93% sensitivity and 89% specificity for detecting the presence or absence of left ventricular dysfunction determined by echocardiography. BNP levels were able to differentiate patients with completely normal ventricular function (38 ± 4 pg/ml) from patients with normal ejection fraction but with wall motion abnormalities (177 ± 20 pg/ml), as well as those with impaired ejection fraction (652 ± 50 pg/ml, P < 0.001). In patients with normal systolic function, a BNP level of greater than 130 pg/ml was 100% sensitive and 100% specific for diastolic dysfunction.

Conclusions: An easy, rapid test for BNP can reliably predict the presence or absence of both levels of left ventricular systolic dysfunction as well as to delineate diastolic dysfunction in those patients with a normal ejection fraction. We believe that BNP may be an excellent screening tool for left ventricular dysfunction, and may, in fact, represent an important adjunct for the diagnosis of diastolic dysfunction.

1027-147 Is Increased Heart Rate Predictive of Poor Survival in Patients With Preserved LV Systolic Function?

Prakash C. Deedwania, Enrique V. Carbajal, Ronna Mallios. VACHCSC, Fresno, CA; UCSF School of Medicine, San Francisco, CA, USA

Heart failure (HF) with preserved LV systolic function (DHF) is becoming an increasing clinical problem. Because of the preserved LV function and lack of significant neurohormonal activation, it is believed that patients with DHF have better prognosis. However, little information is available regarding the prognostic markers in unselected patients with DHF. We recently evaluated the prognostic value of 71 variables including clinical features, LV function data, exercise capacity, and Holter monitoring data in 575 patients followed at our institution from 1992 to 1997. Mean age was 69 ± 10 years, mean LVEF was 38 ± 15%, 64% had ischemic etiology, 79% were on ACE inhibitor, 52% on diuretics, 62% on digoxin, and 65% on other vasodilators. During the five years follow-up, 174 (30%) patients had died, and of all the variables assessed, increased heart rate (HR), elevated BUN, and worsening symptoms were the best predictors of cardiac death. LV function data were available for 510 (89%) patients, and in these, 236 (46%) had DHF (LVEF > 40%). We evaluated if increased HR was as predictive of poor survival in DHF patients as it was in patients with normal LV systolic function (SHF). The mean HR was higher in SHF patients compared to DHF patients (62 ± 13 vs. 78 ± 11, p < 0.001). Thirty-nine percent of SHF patients and 33% of DHF patients died during the five year follow-up. Increased HR was highly predictive (p < 0.0001) of higher mortality in both HF groups. Among the DHF patients, mean HR was significantly higher in those patients who had died compared to the 159 survivors (79 ± 10, p < 0.0001). In the multivariate analyses, increased HR remained a powerful and independent predictor of cardiac death in both HF groups.

Conclusion: Increased HR is equally predictive of poor survival in heart failure patients with preserved LV systolic function.

1027-148 Relation of Left Ventricular Contractile Dysfunction to Left Ventricular Mass in Aortic Valve Disease

Kazuhito Taniguchi, Satonu Kuki, Takaharum Masai, Shuji Endo, K. Yoshiida. Osaka Rosai Hospital, Suitai, Japan

Background: Identifying the transitional stage from physiologic hypertrophy to pathologic hypertrophy has important implications in determining the timing of therapeutic as well as operative interventions for aortic valve disease. To elucidate this transitional stage, we studied the relations of left ventricular contractile performance to left ventricular chamber volume, hemodynamic load and mass.

Methods: Data were obtained from quantitative cineangiography, and pressure measurements in 73 patients with aortic regurgitation (AR) and 39 patients with aortic stenosis (AS). Thirty patients without heart disease served as normal controls. Forty-one patients with AR and 20 patients with AS were reevaluated (average, approximately 23 months) after aortic valve replacement. By using the relation of ejection fraction to end systolic area (afterload-corrected EF), a slightly impaired contractility was defined as < predicted EF - 5 x SD, and a severely impaired contractility as < predicted EF - 10 x SD.

Results: Fourteen of 73 patients with AR and 8 of 39 patients with AS had a slightly impaired contractility, and 36 with AR and 19 with AS had a severely impaired contractility. In multivariate analysis, the most important discriminator of normal, slightly impaired, or severely impaired contractility for all 112 patients was left ventricular mass, rather than left ventricular chamber volume or hemodynamic load (p < 0.05). Left ventricular mass index associated with a slightly impaired contractility was similar in the two patient groups (167 ± 40 g/m² in AR and 194 ± 51 g/m² in AS, respectively, p = NS). Patients with a severely impaired contractility had mostly a left ventricular mass index > 192 g/m², double its normal value (96 ± 13 g/m² for controls). Contractile dysfunction tended to improve, but did not return to normal completely after surgery in both groups, especially in patients with a preoperative mass index > 192 g/m², and moderate to severe LVH persisted.

Conclusion: These findings suggest that LVH becomes pathologic hypertrophy at the similar degree in left ventricular mass index (about double its normal value) for the volume and pressure overload.

1028 Diastolic Cardiomyopathy

Sunday, March 12, 2000, Noon–2:00 p.m.
Anaheim Convention Center, Hall A
Presentation hour: 1:00 p.m.–2:00 p.m.

1029-151 The Expression of Bel-2 Associated Protein X and Bcl-2 in Cardiomyocytes is Related to Left Ventricular Remodeling in Patients With Dilated Cardiomyopathy

Akihira Hirata, Masatake Fukumura, Tsuyoshi Shimonogata, Kazuaki Kumagai, Takahisa Yamada, Hisakazu Ogita, Yoshihiro Asano, Masahito Asai, Noritake Hoké. Osaka Prefectural General Hospital, Osaka, Japan

Background: It is reported that the myocellular cell death in dilated cardiomyopathy (DCM) would be partly related to apoptosis. To clarify the relationship between the apoptosis and the progression in DCM, we examined left ventricular endomyocardial biopsy specimen in 13 patients with DCM diagnosed clinically and pathologically.

Methods: The expression of Bel-2 associated protein X (Bax) and Bel-2 was estimated using immunoenzyme-assayed biopsy specimen. We counted each number of positively stained cell by anti-Bax or Bcl-2 in the mirror section per 10 different high power fields (x400) randomly selected. The progression of left ventricular heart failure was assessed echocardiographically, by comparing left ventricular end-diastolic dimension (LVDd) and ejection fraction (EF) measured at the time of biopsy with those 1 year after. There were no significant correlations between the number of positive cells and age, sex, NYHA classification, LVDd and EF at the beginning, or drugs which the patients received.

Results: The ratio of the number of Bax positive cell and Bel-2 positive cell (Bax/Bcl-2) showed a significant correlation with a % increase of LVDd (r = 0.735, p < 0.005), while it tended to show an inverse correlation with a % increase of EF.

Conclusion: Bax/Bcl-2 would be a predictor of left ventricular remodeling in patients with DCM.
**ABSTRACTS – Cardiac Function and Heart Failure**

**1028-152**

**Peripartum Cardiomyopathy: Analysis of Clinical Outcome, Left Ventricular Function, Plasma Levels of Cytokines and Fas/APO-1**

Karen Silwa, Daniel Skukicky, Anette Bergemann, Geoffrey Candy, Pinhas Sarelle, Heart Failure Research Unit, Department of Cardiology, Baragwanath Hospital, Johannesburg, South Africa

**Background:** previous studies in patients with peripartum cardiomyopathy (PPC) were done when ACE inhibitors and β blockers were not routinely used in heart failure. Inflammatory cytokines play an important role in the pathogenesis and progression of heart failure of other etiologies. However, there is a paucity of data regarding cytokine expression in patients with PPC. Plasma concentrations of Fas/APO-1 receptors (an apoptosis-signalling receptor) have not been reported in this population.

**Objectives:** 1) to evaluate the outcome of patients with PPC on current treatment for heart failure, 2) to assess the circulating plasma levels of cytokines and Fas receptors, and 3) to identify predictors of prognosis.

**Methods:** We followed prospectively 28 consecutive black women with PPC. All patients were treated with diuretics, digoxin, enalapril and carvedilol. Echocardiograms were performed at baseline and after 6 months of treatment. Cytokine and Fas/Apo-1 plasma levels were measured at baseline.

**Results:** 4) Tumor necrosis factor-α, Interleukin-6 and Fas/APO-I levels were significantly elevated in the study patients compared to 20 healthy volunteers. Eight patients died; Fas/Apo-1 levels were significantly higher in patients who died compared to survivors (8.98 ± 4.5 vs 5.3 ± 1.2 U/ml respectively, p = 0.02). At 6 months, ejection fraction improved from 26.7 ± 10 to 42.7 ± 16%, p = 0.00003, with an increment of more than 10 units in 10 patients (26.7 ± 4 to 51.9 ± 8%, p = 0.00006).

**Conclusions:** Cytokine and sFas levels are elevated in patients with PPC. Despite treatment with ACE inhibitors and β blockers, mortality remains high. However, in 34% of the patients, left ventricular function almost completely normalized.

**1028-153**

**Pentoxifylline Improves Left Ventricular Performance in Patients With Idiopathic Dilated Cardiomyopathy Treated With Digoxin, Angiotensin Converting Enzyme Inhibitors and Carvedilol**

Daniel Skukicky, Anette Bergemann, Karen Silwa, Geoffrey Candy, Pinhas Sarelle, Heart Failure Research Unit, Department of Cardiology, Baragwanath Hospital, Johannesburg, South Africa

**Background:** Carvedilol has been shown to improve left ventricular performance in patients with systolic dysfunction already treated with digoxin and ACE inhibitors. The mechanism of beneficial effects mediated by IA remain to be elucidated.

**Methods:** In a prospective, randomized, double blind, placebo controlled study we enrolled 29 consecutive patients (mean age 49 ± 11 years) with idiopathic dilated cardiomyopathy and an ejection fraction < 40% following at least 3 months of therapy with diuretics, digoxin, ACE inhibitors and carvedilol. Patients were randomized to pentoxifylline 400 mg TDS (n = 15) or placebo (n = 14). Echocardiograms and radionuclide studies were performed at baseline and after 6 months.

**Results:** 5 patients died during the study period (3 in the placebo group). Left ventricular dimensions at end-diastole (EDD), end-systole (ESD) and radionuclide ejection fraction (EF) for patients that completed the 6 months period are shown in the table.

<table>
<thead>
<tr>
<th>EDD, mm</th>
<th>Baseline 6 months p</th>
<th>Baseline 6 months p</th>
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<tbody>
<tr>
<td>66 ± 7</td>
<td>66 ± 10</td>
<td>66 ± 10</td>
</tr>
<tr>
<td>66 ± 10</td>
<td>66 ± 10</td>
<td>0.8</td>
</tr>
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</table>

**Conclusion:** The addition of pentoxifylline to background therapy with digoxin, ACE inhibitors and carvedilol further improves left ventricular function in patients with idiopathic dilated cardiomyopathy.

**1028-154**

**Immunohistological Changes During Immunoadsorption Therapy With Subsequent Immunoglobulin Substitution in Dilated Cardiomyopathy**

Alexander Staudt, Frank Schäper, Peter Bramlage, Wolf V. Dörfler, Verena Stangl, Karl Stangl, Gert Baumann, Stephan B. Felix, Department of Internal Medicine, Institute of Pathology, Charité, Humboldt University, Berlin, Germany

**Background:** Immunoadsorption (IA) was performed in 11 patients suffering from dilated cardiomyopathy (DCM) and immunoadsorption is a removal of variable, immunoglobulins from 2.2 to 0.2 to 0.9 to 0.3 ln/mm² (p < 0.01). The underlying mechanisms of beneficial effects mediated by IA remain to be elucidated.

**Methods:** 11 patients with DCM (NYHA III–IV, EF < 30%, stable medication) received IA therapy and subsequent immunoglobulin substitution (0.5 g/kg) at one-month intervals until month 3. Before and after (< 7 d) IA therapy 5 to 8 right ventricular biopsies were obtained from all patients. DCM patients (controls, n = 7, EF < 30%, NYHA III–IV) were treated with conventional therapy only. From these patients biopsies were also obtained in an interval of 3 months. Biopsies were fixed in 4% formalin and embedded in paraffin. The sections were 2 µm thick. The staining procedure with the labeled streptavidin-biotin (LSAB) method was used. The following antibodies were used: anti CD3; -CD4; -CD8; -CD45 RO, HLA-DP. The number of positive cells (cells/mm²) was counted under high power magnification (400x) by two independent observers.

**Results:**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>After IA</th>
<th>p &lt; vs. baseline</th>
<th>p &lt; vs. baseline</th>
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<tbody>
<tr>
<td>CD3</td>
<td>4.5</td>
<td>1.86</td>
<td>2.2</td>
<td>11.6</td>
</tr>
<tr>
<td>CD4</td>
<td>2.3</td>
<td>0.6</td>
<td>1.5</td>
<td>7.2</td>
</tr>
<tr>
<td>CD8</td>
<td>0.01</td>
<td>0.01</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>HLA-DR</td>
<td>0.01</td>
<td>0.01</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>CD45 R0</td>
<td>0.01</td>
<td>0.01</td>
<td>0.05</td>
<td>0.05</td>
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</tbody>
</table>

In controls the number of immunopositive cells and the expression of HLA-DR remained stable during follow up.

**Conclusion:** IA reduces the inflammatory process in myocardium of DCM patients.

**1028-155**

**Circulating Matrixmetalloproteinase in Patients With Dilated Cardiomyopathy**

Takeshi Yamazaki, Jong-Dae Lee, Hirofumi Shimizu, Takanori Ueda, First Department of Internal Medicine, Fukuoka Medical University, Fukuoka, Japan

**Background:** It has been reported that MMP protein content and activity were upregulated in the failing human heart, suggesting that these proteins may contribute to myocardial remodeling. However, there are few reports to describe the level of circulating MMPs in chronic heart failure (CHF).

**Purposes and Methods:** To examine whether the circulating MMPs are also involved in the pathogenesis of CHF, we measured circulating levels of MMP-2, MMP-9 and its inhibitors, tissue inhibitor of metalloproteinase (TIMP-1) using enzyme-linked immunosorbent assay methods in 29 patients with CHF (left ventricular ejection fraction [LVEF] < 50%, 19 men, 66 ± 12 years old). 14 patients with dilated cardiomyopathy (DCM) and 15 with old myocardial infarction (OMI). Eleven age-matched subjects having normal coronary arteries and normal ejection fraction were used as controls (CTL). None had inflammatory signs. No differences were found in the incidence of hypertension and diabetes mellitus, and in lipid profiles among 3 groups.

**Results:** As a whole, LVEF had significant correlations with both MMP-2 (r = −0.79, p < 0.03) and MMP-9 (r = −0.50, p < 0.03). The level of MMP-9 was significantly greater in DCM (111 ± 114 nm/ml) compared to OMI (31 ± 29 nm/ml, p < 0.05) and CTL (24 ± 13 nm/ml, p < 0.05), while the levels of MMP-2 (DCM: 918 ± 616 nm/ml; OMI: 549 ± 236 nm/ml; CTL: 483 ± 172 nm/ml) did not show significant differences among 3 groups. TIMP-1 (DCM: 152 ± 82 nm/ml; OMI: 169 ± 53 nm/ml; CTL: 147 ± 29 nm/ml) was identical in each group. Thus, the ratio of MMP-9/TIMP-1 was significantly greater in DCM (0.71 ± 0.62) than in OMI (0.19 ± 0.15, p < 0.05) and CTL (0.17 ± 0.10, p < 0.05).

**Conclusion:** Our data indicated that MMP-9 production was increased in DCM patients, suggesting a dense relation between this enzyme activity and the degradation of cardiac interstitial tissue.
1028-156  
**Association Between Aldosterone Synthase Gene Polymorphism and Left Ventricular Size in Patients With Congestive Heart Failure**

Eiji Takeda, Hozuka Atsuki, Kenji Kanazawa, Nobuyuki Shiga, Masahide Goto, Shinya Yoshida, Yasushi Matsuoka, Chihiko Iwai, Hiroya Kawai, Akira Takahashi, Hirokiyuki Kuguro, Mitsuhiro Yokoyama. The First Department of Internal Medicine, School of Medicine, Kobe University; *Hei gay Cardiovascular Center, Japan*

**Background:** Cardiac steroidogenic system is postulated to play an essential role in cardiac remodeling. Previously, aldosterone synthase (CYP11B2) gene T (-344) C promoter polymorphism, which modulates its transcription, was reported to be associated with left ventricular (LV) characteristics in normal subjects. However, it has not been explored whether the relationship between this polymorphism and LV characteristics exists in patients with heart failure.

**Methods:** To investigate the relation between this polymorphism and LV characteristics in failed heart, we assessed the T (-344) C genotype, the hemodynamic parameters, and LV end diastolic and systolic volume index (EUVI, ESVI) in 183 dilated cardiomyopathy (DCM) patients. We also analyzed serum aldosterone, plasma renin level and the semi-quantitative assessments of fibrosis from biopsy specimens. We further conducted a case-control study to elucidate whether this polymorphism can be a genetic risk factor for DCM.

**Results:**  
- T & CC genotype had significantly larger LV size and smaller cardiac index (CI) than TT genotype.
- Whereas, biochemical and histological data were not different between TT and TO + CC.

**Conclusion:** The T (-344) C CYP11B2 promoter polymorphism could modulate the dilative cardiac remodeling in patients with congestive heart failure due to DCM.

1028-157  
**Coxsackie B Virus RNA Replication in the Myocardium of Patients With End-Stage Idiopathic Dilated Cardiomyopathy**

Shigekazu Fujoka, Yasushi Kitaura, Fumio Terasaki, Akira Ukimura, Hirofumi Deguchi, Kaeihiro Kawamura, Akira Shimoizumi, Tadao Ishimura, Hisayoshi Suma. Osaka Medical College, Takatsuki; Shonan Kamakura General Hospital, Kamakura, Japan

**Background:** Molecular biological techniques have demonstrated the importance of enteroviruses (EVEs) in the pathogenesis of dilated cardiomyopathy (DCM). Recently, associations of hepatitis C virus or adenovirus with DCM have been reported. We evaluated viral infection of the myocardium from DCM patients, and dilated cardiomyopathy (DCM).

**Methods:** From 24 patients with idiopathic DCM, 23 patients with ischemic heart disease (IHD), 2 hypertrophic cardiomyopathy patients (HCM) and 2 patients with valvar disease near asease (VHD) were snap frozen at explantation. RNA for enteroviral, adenoviral or CMV sequences was extracted using Trizol, reverse transcribed using random hexamer and superscript II and CDNA used in nested PCR, with myoglobin mRNA as the housekeeping gene. Amplification of human CMV and adenovirus sequences was performed using nested PCR following DNA sequencing.

**Results:** Mean age of DCM patients undergoing transplantation was 41.2 (±8.1) years v 50.7 (±5.7) years in IHD, HCM and VHD patients. There was no significant difference between LV end diastolic dimension (7.1 mm v 7.3 mm), fractional shortening (12.2 v 12.4%), or NYHA class (3.7 v 3.8) between DCM patients and controls. Five DCM patients had a clinically suspected viral etiology. Mean time from diagnosis to transplantation in DCM patients was 1.8 (+1.6) years. Among DCM patients histology demonstrated typical fibrosis and myocyte changes in 75% and was atypical in 25%. There were no cases of acute or chronic myocarditis. Double-blind screening of random wells demonstrated an in-house sensitivity for detection of viruses of 1 gene fragment/assay. Despite this, enteroviral, adenoviral or CMV sequences were detectable neither in DCM patients nor controls.

**Conclusion:** Viral persistence is not detectable in end stage DCM.

1028-158  
**Frequency of Viral Persistence in End-Stage Dilated Cardiomyopathy**

Niall G. Mahon, Paul Ristley, Behnam Zal, Christina Baboonian, Michael J. Davies, William J. McKenna. St George’s Hospital Medical School, London, UK

**Background:** Conflicting data is available on the importance of viral infection in idiopathic dilated cardiomyopathy (DCM) that may partially be explained by variations in illness duration prior to viral testing. Recent work has demonstrated a high frequency of detectable myocardial viral sequences shortly after presentation. The aim of this study was to determine the frequency of persistence of enteroviral, adenoviral and cytomegaloviral (CMV) genetic material in the myocardium in end-stage DCM.

**Methods:** 2-3 mm samples from the left ventricle (LV) and septum of explanted hearts of 24 DCM patients, 23 patients with ischaemic heart disease (IHD), 1 hypertrophic cardiomyopathy patient (HCM) and 2 patients with valvar disease near asease (VHD) were snap frozen at explantation. RNA for enteroviral, adenoviral or CMV sequences was extracted using Trizol, reverse transcribed using random hexamer and superscript II and CDNA used in nested PCR, with myoglobin mRNA as the housekeeping gene. Amplification of human CMV and adenovirus sequences was performed using nested PCR following DNA sequencing.

**Results:** There was no evidence of other virus infection in DCM hearts. Active viral RNA replication appeared to be present in a significant proportion of these cases. Minus-strand coxsackieviral RNA in the myocardium may be a marker for poor clinical outcomes after PLV. There was no evidence of other virus infection in DCM hearts.

1028-159  
**Hypercholesterolemia is Associated With Impaired Aerobic Capacity in Patients With Dilated Cardiomyopathy: Normalizing Effects of Chronic Exercise Training**

Josef Niemauer1,2, Katharine Waggie-Papic1, Andrew J.S. Coats1,2, NHLL, London, UK; 2University of Leipzig–Heart Center, Germany

**Background:** We have previously shown in mice that hypercholesterolemia is associated with an impaired oxidative capacity and that this can be normalized by exercise training. In the present study we set out to assess whether these effects can also be found in patients with mild hypercholesterolemia and dilated cardiomyopathy.

**Methods:** 21 patients and 9 healthy volunteers were randomly assigned to 8 weeks of exercise (>5 ×/wk, ergometer training. 30 min/d, cardioresistance 9 min/d) followed by 8 weeks of rest, and vice versa (cross-over study). Plasma nitrite and nitrate (NOx) concentrations were measured by Griess reaction.

**Results:** After rest, there was an inverse correlation between cholesterol and mVO2 in patients who were not prescribed oral nitrates as part of their regular medical treatment (r = 0.534, p < 0.0051) and healthy volunteers (r = 0.707, p < 0.04). This was lost after exercise training due to an improved mVO2 (r = 0.685, p = 0.0061), which was neither seen in patients who were taking oral nitrates (r = 0.330, p = 0.2781) and it was never seen in patients who were taking oral nitrates (r = 0.413, p < 0.0005). In keeping with these observations, an inverse correlation was noted for plasma NOx levels and anaerobic threshold in patients after rest (r = 0.780, p = 0.0005) and this was again lost after exercise training (r = 0.108, p = 0.7316) and not found in patients on oral nitrates (r = 0.082, p = 0.9343) or healthy volunteers.

**Conclusion:** This study provides evidence in humans that already mild hypercholesterolemia may be associated with an impaired aerobic capacity, possibly via an NO-antagonizing effect.
Effect of Race in Outcomes After Heart Transplantation

University of California at Los Angeles, Los Angeles, California, USA

Background: Multicenter studies in both heart and kidney transplant recipients have suggested that recipient race has an impact on survival. Specifically, the black race appears to have lower survival, however this is controversial. Therefore, we performed this large single center study with standardized pre-operative care to assess the impact on race on outcomes after heart transplant.

Methods: Between December 1996 and January 1999, 770 adult heart transplant patients underwent heart transplant at a single institution. Patients were divided by race into various groups where outcomes of survival and freedom from rejection were determined. 5 year actuarial survival data is expressed.

Results: 702 adult heart transplant patients on triple drug immunosuppression (no cytolytic induction) were divided into the following racial groups: White (n = 556), Black (n = 69), Asian (n = 40), and Hispanic (n = 37). 5 year actuarial survival was not significantly different among the four ethnic groups (White 71%, Black 70%, Asian 73%, Hispanic 73%). However, frequency of acute rejection was significantly different between the white vs. black group (59% vs. 51%, p = 0.003). The Asian group had significantly more patients free of rejection compared to the white group (p < 0.001). Other group combinations did not show statistical difference mostly due to relative small numbers of the groups.

Conclusion: Ethnic race appears to have an effect on rejection after heart transplantation, however this factor does not appear to affect overall survival. This suggests that ethnic heterogeneity may be enough to tend toward rejection, however rejections appear to be well tolerated, not leading to mortality. Psychosocial factors such as socioeconomic status, medical compliance in addition to immunological factors do not appear to play a role in outcome but are not evident in mortality outcome in this study.

Independent Prospective Validation of a Clinical Index to Predict Survival in Ambulatory Patients Referred for Cardiac Transplant Evaluation

Marco Bobbio, Singh Dogliani, Giuseppe Giacomarra, Keith D. Aaronson.
University of Turin, Turin, Italy; University of Michigan, Ann Arbor, Michigan, USA

The Heart Failure Survival Score (HFSS) is derived from 7 commonly obtained clinical measures, and may be grouped into 3 HFSS Strata, which classified patients into these HFS Strata: high risk 2 (1.9%); medium risk strata vs. 96 ± 2% for the low risk stratum (p = 0.0005). In addition, there was also a significant difference between the patients after cardiac transplantation and normal subjects (4.40 ± 1.49 versus 9.75 ± 3.01, p < 0.001) indicating impaired peripheral vasculature endothelial function despite transplantation.

Conclusions: Attenuated brachial artery flow-mediated vasodilation and endothelial function in patients with severe congestive heart failure appears to persist after cardiac transplantation.

Modulatory Impact of Diabetes Mellitus on Doppler Derived Indices of Mitral Inflow in Heart Transplantation

Archad A1, Frank Smart,2, Haider Vantoura,3, Maniapple Mahary2, St John Hospital, Detroit, Michigan; 2Tulane University Medical Center; 3Ochsner Clinic, New Orleans Louisiana, USA

Background: Abnormalities in diastolic function are frequently noted in heart transplant recipients. We studied the independent impact of diabetes mellitus (DM) on the indices of diastolic function in cardiac allograft recipients.

Methods: 42 cardiac allograft recipients, 24 diabetes (57%) with normal systolic function and without angiographic evidence of epicaldial coronary arterial disease, were evaluated. 2D echo/Doppler was performed within 8 h after heart catheterization/endocardial biopsy. Ejaculation fraction (EF), wall thickness, and ventricular diameter were measured. PW Doppler across mitral inflow was used to calculate flow weighted relaxation time (IVRT). E/A ratio and deceleration time (DT). Left ventricular mass index (LVMi) was obtained. Doppler (Bx) scores were calculated according to previously defined formula. All studies were performed after 1 month (early) and 12 months (late) following transplantation.

Results: Both groups were matched for heart rate, pre-load and after-load at the time of HHC. There was no difference between the diabetics and non-diabetics in EF, diastolic function, or LVMi, at the early time point. The late results are shown:

<table>
<thead>
<tr>
<th>LATE</th>
<th>EF</th>
<th>A</th>
<th>IVRT</th>
<th>DT</th>
<th>LVMi g/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic n = 24</td>
<td>68 ± 4</td>
<td>1.5 ± 0.5</td>
<td>74 ± 22</td>
<td>94 ± 40</td>
<td>91 ± 34</td>
</tr>
<tr>
<td>Non diabetic n = 18</td>
<td>68 ± 4</td>
<td>1.9 ± 0.5</td>
<td>81 ± 22</td>
<td>108 ± 46</td>
<td>83 ± 13</td>
</tr>
<tr>
<td>P Value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS &lt; 0.05</td>
<td>NS</td>
</tr>
</tbody>
</table>

The Bx score for diabetics was 0.8 ± 0.3 and for non-diabetics was 0.8 ± 0.6 (NS) There was a negative correlation between Bx Score and DT (r = -0.4, p = 0.009).

Conclusion: Our data alludes to a possible modulatory impact of DM on indices of left ventricular diastolic function, with development of relaxation abnormality over time. The concerted impact of episodes of allograft rejection and DM contributes to the development of restrictive diastolic dysfunction. Implantation of a non-diabetic heart in a diabetic recipient may serve as a human model to study the impact of DM over time on myocardial function.
Impact of New UNOS Listing Categories on Cost and Outcome Pre-Transplant

Helen Hauft, Simon Maybaum, Niloo Edwards, Donna Manconi. Columbia University, New York, New York, USA

Background: On January 20th 1999 UNOS listing regulations changed allowing stable patients on inotropic support (status 18) to be discharged home until cardiac transplant. From 1/01/00 through 1/01/01, 49 patients have been prioritized as status 18 at our institution. Of these candidates, 30 patients were discharged home. Criteria for discharge were hemodynamic stability on low dose, minimal inotrope defined as dobutamine at < 7.5 mg/kg/min or milrinone < 0.5 mg/kg/min.

Methods: Cost saving, readmissions and events at home were collected prospectively. Cost saving per patient was calculated as the hospital charge per day minus daily home care costs.

Results: There were 22 males, 8 females with mean age 54 ± 10 yrs. 20 patients had dilated cardiomyopathy, 8 ischemic heart disease, and 2 patients had transplant coronary artery disease. 12 patients received milrinone at a dose of 0.45 ± 0.16 µg/kg/min and 18 patients received dobutamine at a dose of 3.5 ± 1 µg/kg/min. Patients were at home for 47 ± 49 days. Mean cost saving/patient was $70,000. There were 27 readmissions with a mean stay of 8 ± 6 days. 8 patients required more than 1 admission. 52% of admissions were for worsening CHF, 33% for infection or occlusion of the indwelling intravenous line. 11 patients wore a LIFECOR external defibrillator vest for 253 ± 228 hours. 2 patients died suddenly at home, one patient received milrinone 0.5 µg/kg/min and the other dobutamine 3 µg/kg/min.

Conclusions: Significant cost saving is achieved with home inotropic therapy while awaiting cardiac transplant. Mortality remains low but readmission rate is high. Improved continuous intravenous delivery systems may significantly reduce the number of readmissions and further reduce costs.

Chagas' Heart Disease: An Etiology Associated With Better Survival After Heart Transplantation in Comparison With Ischemic and Idiopathic Etiologies

Edimar A. Bocchi, Alfredo Fiorelli. Transplantation and Heart Failure Clinic, Heart Institute, Sío Paulo University Medical School, São Paulo, Brazil

Results of heart transplantation may be influenced by many factors including etiology. We investigated the influence of age, sex, etiology, period of heart transplantation, and results of heart transplantation and causes of death in a nationwide study.

Methods: 1555 patients who underwent heart transplantation, from June 1984 to April 1999 in 16 centers were included in this study. 632 male, age ≤ 7 years 30 pts, from 7 to 30 years 125 pts, from 30 to 60 years 568 pts, > 60 years 56 pts, and the etiology was idiopathic dilated cardiomyopathy in 15% of the pts. during follow-up.

etiology, postoperative bleeding in ischemic, graft coronary artery disease and graft dysfunction in idiopathic. Reactivation of Chagas' disease occurred in 15% of the pts. during follow-up.

Conclusions: Significant cost saving is achieved with home inotropic therapy while awaiting cardiac transplant. Mortality remains low but readmission rate is high. Improved continuous intravenous delivery systems may significantly reduce the number of readmissions and further reduce costs.

Clinical Patterns of Recurrence of Tobacco Smoking in Prior Smokers Undergoing Heart Transplantation

Ananth Presad, Mandeep R. Mehra, Patricia A. Uber, Robert L. Scott, Myung H. Park, Ochsner Heart and Thrombosis Center, New Orleans, LA, USA

Background: While most transplant programs emphasize smoking cessation, little information exists on risk factors for return to tobacco abuse. We sought to identify risk factors to smoking and clinical predictors for recurrence of tobacco smoking in heart transplant recipients who had demonstrated compliance with smoking cessation prior to transplantation.

Methods: We prospectively examined 50 heart transplant recipients with admitted pre-transplant smoking history, and established compliance with pre-transplant smoking cessation prior to transplantation.

Results: There were 22 males, 8 females with mean age 54 ± 10 yrs. 20 patients had dilated cardiomyopathy, 8 ischemic heart disease, and 2 patients had transplant coronary artery disease. 12 patients received milrinone at a dose of 0.45 ± 0.16 µg/kg/min and 18 patients received dobutamine at a dose of 3.5 ± 1 µg/kg/min. Patients were at home for 47 ± 49 days. Mean cost saving/patient was $70,000. There were 27 readmissions with a mean stay of 8 ± 6 days. 8 patients required more than 1 admission. 52% of admissions were for worsening CHF, 33% for infection or occlusion of the indwelling intravenous line. 11 patients wore a LIFECOR external defibrillator vest for 253 ± 228 hours. 2 patients died suddenly at home, one patient received milrinone 0.5 µg/kg/min and the other dobutamine 3 µg/kg/min.

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Methods: 1555 patients who underwent heart transplantation, from June 1984 to April 1999 in 16 centers were included in this study. 632 male, age ≤ 7 years 30 pts, from 7 to 30 years 125 pts, from 30 to 60 years 568 pts, > 60 years 56 pts, and the etiology was idiopathic dilated cardiomyopathy in 407 pts, ischemic in 190 pts, transplant coronary artery disease in 117 pts, vascular in 29 pts, congenital in 14 pts, peripartum in 12 pts, hypertrophic in 7 pts, retransplantation in 6 pts, restrictive in 5 pts, alcoholic in 4 pts, and drug in 1 pt.

Results: The survival rate at 1, 4 and 8 years was 66%, 54% and 40%, respectively. Survival improved from 1990 to 1999 (p < 0.0001), and it was better in chagasic etiology compared with idiopathic and ischemic (p < 0.02) (Fig 1). Sex and age didn't influence survival. Regarding the causes of death: rejection and neoplasia were more common in chagasic etiology, postoperative bleeding in ischemic, graft coronary artery disease and graft dysfunction in idiopathic and ischemic. Reactivation of Chagas' disease occurred in 15% of the pts. during follow-up.

In conclusion: The etiology can influence the survival and causes of death. Chagasic cardiomyopathy is a defined indication for heart transplantation with better results in comparison with other etiologies.
The expression of the pro-apoptotic oncogene, Bax, as assessed by reverse transcriptase-polymerase chain reaction, may be mediated via oxidative stress and myocardial BAR downregulation. The purpose of this study was to determine whether exposure to AASs produced by multiple intracoronary microemulsions, which, in turn, was significantly attenuated after inhibition of p38 MAPK. AASs induced apoptosis may be implicated in the pathogenesis of cardiomyopathy, and sudden cardiac death. AASs exert direct toxic effects on cardiomyocytes.

Background: We previously showed that exposure of failed cardiomyocytes to angiotensin-II (A-II) or to hypoxia (HX) leads to overexpression of p38 MAPK. In the present study, we hypothesized that inhibition of p38 MAPK will rescue failed cardiomyocytes from HX or A-II-mediated apoptosis.

Methods: Studies were performed in cardiomyocytes isolated from 5 dogs with chronic heart failure (HF). The effect of intravenous administration of ethanol (50 mM) on cardiomyocyte viability was evaluated. Cardiomyocytes were exposed to HX (95% N2, 5% CO2) or to A-II (0.5 nM) for 3 hours in the presence (5 µM) and absence of the p38α inhibitor SB 203580 (Inh).

Results: Apoptotic cell death was significantly reduced after inhibition of p38 MAPK. The data are shown in the table.

<table>
<thead>
<tr>
<th>Condition</th>
<th>p38α + Inh</th>
<th>p38α - Inh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline + Trolox</td>
<td>145 ± 15</td>
<td>107 ± 7</td>
</tr>
<tr>
<td>Saline + A-II</td>
<td>183 ± 25</td>
<td>100 ± 5</td>
</tr>
<tr>
<td>Saline + HX</td>
<td>150 ± 12</td>
<td>72 ± 11</td>
</tr>
</tbody>
</table>

Conclusions: Exposure of failed cardiomyocytes to HX or A-II enhanced apoptosis in ethanol-treated groups (P < 0.05). Ethanol exposure appeared to involve mitochondrial damage via an increase in oxidative stress and release of cytochrome c, which activates caspases that initiate chromatin fragmentation and apoptosis. Antioxidants markedly inhibited oxidative stress and myocyte apoptosis in ethanol-treated groups (P < 0.05).

1048-145 Oxidative Stress in Ethanol-Induced Cardiomyocyte Apoptosis

Zhenli Guan, Charles Y. Liu, Eugene Morkin, Ciemond D. Eskelson. University Heart Center, University of Arizona, Tucson, AZ 85724, USA

Background: Previous studies have shown that alcohol induces myocardial damage via a reactive oxygen intermediate (ROI) pathway.

Methods: To determine whether ethanol induces apoptosis in neonatal cardiomyocytes, cardiomyocytes from 1 to 2 day-old Sprague-Dawley rats were treated with ethanol at 0 mM, 20 mM, 100 mM and 200 mM for 0, 1, 4, 8, 16, and 24 h. α-Tocopherol and ascorbic acid (2 mM) and ascorbic acid (2 mM) were added to medium 1 h before addition of ethanol. Apoptosis was measured by transmission electron microscopy, fluorescence microscopy, and flow cytometry. Intracellular glutathione was measured by fluorescence microscopy. Production of ROI was detected by fluorescence microscopy and flow cytometry. Mitochondrial membrane potential (MMP) was measured by laser confocal microscopy and flow cytometry. Cathepsine C was assayed by immunocytochemistry and caspase-3 activity was measured by colorimetry.

Results: Histologically, typical apoptosis was found with chromatin condensation, membrane blebbing, shrinkage and cyttoplasm condensation. Apoptosis was concentration-dependent (P < 0.001). Both α-tocopherol and ascorbic acid inhibited oxidative stress and cardiomyocyte apoptosis in ethanol treated groups (P < 0.05).

Conclusion: Our data indicated that ethanol induced cardiomyocyte apoptosis at 200 mM and necrosis at 2000 mM. The mechanism of action appeared to involve mitochondrial damage via an increase in oxidative stress and release of cytochrome C, which activates caspases that initiate chromatin fragmentation and apoptosis. Alcohol-induced myocardial apoptosis is a result of increased oxidative stress and apoptosis induced by ethanol.
**1048-147** Endothelin-1 Supresses Nitric Oxide Induced Caspase-3 Activation and Antagonizes Apoptosis in Cardiomyocytes

Michihiko Hirose, Masayoshi Shichiri, Shigeru Ishiyama, Takashi Shimoo, Shinji Abe, Susumu Adachi, Mirei Tanamori, Hiroshi Ito, Yukio Hitara, Fumaki Marumo. Tokyo Medical and Dental University, Women's Medical University, Tokyo, Japan

**Background:** Endothelin-1 (ET-1), an endothelin-derived vasoactive peptide, functions as a potent growth factor of cardiomyocytes, leading to hypertrophy. In contrast, nitric oxide (NO) has been shown to cause apoptotic death of cardiomyocytes. In the present study, we studied the mechanisms of inhibition by ET-1 of NO-induced apoptosis in cultured neonatal rat cardiomyocytes.

**Methods and Results:** Addition of S-nitroso-N-acetylpenicillamine (SNAP), a NO donor, induced a fraction of cells undergoing apoptosis determined by TUNEL staining on terminal deoxy-nucleotidyl transferase-mediated dUTP-biotin nick-end labeling, and measurement of caspase-3 and -9 enzyme activities. The effect of ET-1 was examined using an ET-A receptor antagonist or SNAP administration which was inhibited by coinubcation with ET-B receptor antagonist.

ET-1 inhibited NO-induced caspase-3 activation and apoptosis, and the effect was blocked by incubation with ET-A receptor antagonist (BQ223) but not with ET-B receptor antagonist (BQ788). Western blot analysis revealed ET-A and ET-B protein expression following SNAP administration which was inhibited by coinubcation with ET-A, whereas BQ-2 was unaffected by ET-B receptor antagonist.

**Conclusion:** These data demonstrate the inhibitory effect of ET-1 on NO-induced caspase-3 activation and subsequent apoptosis via the ET-A receptor in cardiomyocytes, suggesting a cell-protective role for ET-1 in the event of NO production in cardiomyocytes.

**1048-148** Exposure of Isolated Canine Failed Cardiomyocytes to Angiotensin-II is Associated With Overexpression of FasL, That Is Reversed by Inhibition of p38 α/β MAPK

Anastassia Todor, Victor G. Sharov, Sudesh Mishra, Takayuki Mishima, Pervez Chaudhry, Omar Nasa, Sidney Goldstein, Hari N. Sabbath. Henry Ford Heart and Vascular Institute, Detroit, Michigan, USA

**Background:** Long-term stress with ACE inhibition has been shown to attenuate cardiomyocyte apoptosis in animals with heart failure (HF). The mechanism by which ACE inhibition rescues cardiomyocytes from apoptosis remains unclear. In this study, we tested the hypothesis that exposure of cardiomyocytes to angiotensin-II (A-II) leads to overexpression of FasL, Fasl, against A-II, present on cardiomyocytes, promotes apoptosis-3 and proapoptotic Bax protein expression following SNAP administration which was inhibited by coinubcation with ET-A receptor antagonist. The regulation of caspase-3/9, NO, and ET-1 was further confirmed by measurement of caspase-3 enzyme activity. The inhibitory effect of ET-1 on NO-induced caspase-3 activity was not abrogated by pretreatment with a MAP kinase-kinase-1 inhibitor, PO98059.

**Conclusion:** These data demonstrate the inhibitory effect of ET-1 on NO-induced caspase-3 activation and subsequent apoptosis via the ET-A receptor in cardiomyocytes, suggesting a cell-protective role for ET-1 in the event of NO production in cardiomyocytes.

**1048-149** Apoptosis in Skeletal Muscle of Patients With Chronic Heart Failure: Role of Inducible Nitric Oxide Synthase and IL-1β Expression

Volker Adams, Rainer Hambrecht, Hong Jiang, Sven-Mobus-Winkel, Gerhard Schuler. University Leipzig – Heart Center, Department of Cardiology, Leipzig, Germany

**Background:** Recently, apoptosis (Ap) of skeletal muscle (SM) myocytes was detected in animal models of chronic heart failure (CHF) and in patients (pts) with CHF. Several in vitro studies demonstrated that inflammatory cytokines and high concentrations of nitric oxide (NO) are potent agents to induce Ap. It is still unknown which factors induce apoptosis in SM of patients with CHF. Therefore, we analyzed the expression of inflammatory cytokines and inducible nitric oxide synthase (iNOS) in SM of patients with CHF and correlated these factors with the occurrence of Ap.

**Methods:** SM biopsies (m.vastus lateralis) of 39 CHF pts (NYHA II-III) and age-matched healthy controls were analyzed by TUNEL for the presence of Ap and by quantitative immunohistochemistry for iNOS, TNF-α, IL-1β, and IFN-γ. Four sections of each biopsy were screened for apoptotic nuclei. A sample with at least 2 positive nuclei per section was classified as positive.

**Results:** Ap was detected in 15/39 (38%) CHF-pts and in none of the controls. Pts with Ap positive SM exhibited a significant lower VO2max (15.5 ± 9.0 vs 19.8 ± 9.0 ml/kg min; p = 0.004), a higher iNOS expression (5.6 ± 0.8 vs 2.3 ± 0.3% positive tissue area; p < 0.001) and a higher IL-1β expression (4.1 ± 0.1 vs 1.0 ± 0.08% positive tissue area; p = 0.02) compared with pts exhibiting Ap negative SM biopsies. No difference was detected between Ap positive and negative SM with respect to local expression of TNF-α and IFN-γ.

**Conclusion:** For the first time, a correlation between IL-1β expression and Ap could be detected in SM of pts with CHF. This suggests that IL-1β and iNOS are possibly involved in the regulation of Ap, finally contributing to a reduced exercise capacity.
POSTER

1049  | Cytokines and Natriuretic Peptides in Heart Failure: Diagnostic and Therapeutic Implications

Sunday, March 12, 2000, 4:00 p.m.–5:00 p.m. 
Anaheim Convention Center, Hall A 
Presentation Hour: 5:00 p.m.–6:00 p.m.

1049-151 | A Rapid Bedside Test for Brain Natriuretic Peptide: Accurately Predicts Time to Response and Clinical Outcomes in Patients Admitted With Decompensated Heart Failure

Van L. Cheng, Radmila Kasanegra, Nancy Gardetto, Alan S. Maisel. VAMC and UCSD, La Jolla, CA, USA

Background: While therapy for patients with decompensated congestive heart failure (CHF) often leaves patients feeling better, there are no objective measures of improvement that correlate with the short-term outcomes of mortality and readmission. Because brain natriuretic peptide (BNP) reflects both left ventricular stretch as well as neurohormonal modulation, we hypothesized that this peptide would be useful in assessing therapeutic responses and outcomes in patients admitted with decompensated CHF.

Methods: BNP was measured daily (Biosite Diagnostics, La Jolla, CA) during patient referral (intomnps, vasodilators, diuretics) in 49 patients admitted with decompensated NYHA class IV CHF. Discharge BNP levels as well as the change in BNP levels were related to subsequent end-points, which included mortality (during hospitalization) and readmission within 30 days.

Results: Of the 49 patients admitted with decompensated CHF, fifteen end-points occurred (death = 9; readmission = 6-7). The delta BNP change during treatment was (-) 1027 pg/ml in patients without an end-point and (+)156 pg/ml in patients with end-points (P < 0.001). No end-points occurred in those patients whose discharge BNP level was less than 900 pg/ml. Of the 21 patients whose discharge BNP level was greater than 900 pg/ml, 15 (71%) developed an end-point. Patients whose discharge BNP was greater than 900 pg/ml were hospitalized longer (17.5 vs. 7.9 days) and had less of a decrease in NYHA with therapy (-0.4 vs. -1.2) than patients with discharge BNP less than 900 pg/ml. Of the eight patients who died in the hospital, only one had a decrease in BNP levels during treatment.

Conclusions: In patients admitted with decompensated CHF, changes in BNP levels both during treatment and at discharge are strong predictors for mortality and early readmission. The results of this study further suggest that therapy for decompensated heart failure should be tailored to decreasing the BNP level during hospitalization.

1049-152  | Usefulness of a Rapid, Bedside Test for Brain Natriuretic Peptide in the Evaluation of Patients Presenting to the Emergency Room With Possible Congestive Heart Failure

Uyen Oao, Heima KrishnaWamy, Radmila Kasanegra, Raimbd Aminovin, Alan S. Maisel. VAMC and UCSD, La Jolla, CA, USA

Background: Congestive heart failure (CHF) is commonly misdiagnosed in the emergency room (ER) setting. In part because of the poor specificity and/or sensitivity of signs and symptoms. Because brain natriuretic peptide (BNP) is released only in setting of left ventricular (LV) strain, we hypothesize that it might be useful as a diagnostic marker in the emergency room setting.

Methods: We evaluated 100 patients who presented to the ER with signs or symptoms possibly compatible with CHF (dyspnea, edema, weight gain, etc.). BNP was measured (Biosite Diagnostics, La Jolla, CA) and the results were blinded from both ER physicians, who made diagnoses at the time of disposition, and 2 cardiologists who made the final diagnosis, taking into account the results of subsequent tests (echos, lung function tests, etc.).

Results: Specificity and sensitivity of usual signs of CHF were: jugular venous pressure: 92% and 34%; third heart sound: 90% and 26%; radi: 82% and 29%. BNP was, however, the single best predictor for diagnosing CHF. In patients with a final diagnosis of CHF, BNP level was 630 ± 77 pg/ml vs. 37 ± 4 pg/ml in patients without CHF (P < 0.001). At a BNP cutoff value of 100 pg/ml, specificity was 98% and sensitivity was 90%. Patients with a final diagnosis of pulmonary disease (bronchitis, pneumonia, asthma) had BNP levels of only 30 ± 2 pg/ml vs. 645 ± 77 pg/ml for patients with CHF (P < 0.001). In patients presenting with edema, BNP was 57 ± 8 pg/ml in patients with no CHF vs. 670 ± 104 pg/ml when CHF was present. All ten patients missed diagnosed by ER personnel would have been correctly identified by BNP levels.

1049-154  | The Cardiac Hormone BNP is a Marker for Left Ventricular Hypertrophy in Dialysis Patients

Alessandro Cataliotti, Michihisa Jougasaki, Hanna Leskinen, Denise M. Houeisen, Lorenzo Massino1, ignazio sieniauova1, Giuseppe Giaconia1, Saverio Parlongoa, Giovanni Tripepi', Carmine Zoccalis, John C. Burnett Jr., 1st lineo di Clinica Medica Luigi Condoreli, Catania; "Division of Nephrologia, Reggio Calabria, Italy; Mayo Clinic and Foundation, Rochester, Minnesota, USA

Background: the cardiac hormone BNP was isolated from hog heart, and its genomic sequence was subsequently identified. The natriuretic peptides are an interesting group of hormones with a role in the regulation of many cardiovascular parameters, such as heart rate, venous return, and arterial pressure. Since then, the BNP gene has been cloned and characterized, and several BNP-related peptides have been identified. These peptides are known as natriuretic peptides (NPs), and they are divided into three categories: atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP).

Methods: Ventilatory and plasma ANP & BNP responses were assessed in 24 patients with LVD, 25 patients with HF (NYHA classes II–III) and 16 normal subjects during symptom-limited cardiopulmonary exercise testing. The increment in plasma BNP was divided by the increment in VO2 (mmol/kg) and this BNP-Ex Ratio (BNP/VO2) was compared among the three groups. We used this ratio as an index of exercise BNP response normalized by the exercise tolerance.

Results: see Table (mean ± SEM, *p < 0.05 vs Normal, #p < 0.05 vs LVD).

Conclusion: These data showed that the augmented BNP-Ex Ratio became apparent in patients with LVD and progressively higher in HF, suggesting that augmented exercise BNP ratio exists early in the course of developing HF.
Conclusions: These studies demonstrate that in dialysis patients the elevation of plasma BNP is associated with altered cardiac structure whereas a normal BNP suggests the absence of LVH. Thus, BNP as compared to the other known NP serves as a serum marker for LVH that is a major risk factor for increased morbidity and mortality in dialysis patients.

![Image](image_url)

1040 155 Neprilysin Inhibitor Therapy for Decompensated CHF Is Not Proarrhythmic
Andrew J. Burger1, George Dennish III, Jay Dinenman, Darlene P. Horton, Michael J. Konstam, Guillermo Torre2. 1Beth Israel Deaconess Hospital, Boston, MA; 2Baylor College of Medicine, Houston, TX, USA

Background: Neprilysin (NEP) is a serine protease that inactivates brain natriuretic peptide (BnP) and other natriuretic peptides. NEP levels are increased in patients with heart failure (HF) and high NEP levels are associated with worse outcomes. IC215, a NEP inhibitor, improved LV systolic function and NEP expression in vitro and in vivo. We sought to determine if IC215 improved outcomes in patients with HF by increasing NEP levels.

Methods: 67 patients with LVEF <40% and NYHA class III or IV HF were prospectively randomized to IC215 (n=34) or placebo (n=33). At 12 weeks, 13 of 17 IC215 patients (76%) and 7 of 16 placebo patients (44%) showed improvement in LV EF (p=0.04). The IC215 patients also showed a significant decrease in echocardiographic markers of LV remodeling (p=0.02 for all comparisons, Table)

Results: 1049-157 Salutary Effect of Exogenous Atrial Natriuretic Peptide on Left Ventricular Relaxation in Patients With Left Ventricular Hypertrophy
Yoichi Kijima, Katsuya Hata, Hideyuki Kohzaka, Hirona Kawali, Yoshikio Shinke, Masakazu Nanashiki, Hideaki Okubo, Takemi Muruta, Soichiro Ota, Mitsuhiro Yokoyama. Kobe University Hospital, Kobe, Japan

Background: Effects of atrial natriuretic peptide (ANP) on vascular system have been well investigated. However, direct effects of ANP on myocardial contractile and diastolic function, especially in pathological condition, has not been well elucidated. The aim of this study was to assess the effects of exogenous ANP on left ventricular (LV) systolic and diastolic functions in patients with LVH.

Methods: 6 patients with LVH (5 hypertrophic cardiomyopathy, 1 hypertension, mean LV ejection fraction 53%) were enrolled in this study. We measured LV systolic and diastolic pressure (ESVP and EDP), stroke volume, relaxation (tau), contractility (Emax, LV diastolic pressure at the slope of the end-systolic pressure-volume relationship), and arterial afterload (EA, effective arterial elastance calculated as ESP/SV) before and after intravenous infusion of low and high dose (0.02 and 0.1 μg/kg/min) of ANP, using manomotor tip conductance catheter with atrial pacing to keep heart rate constant.

Results: ANP significantly improved LV relaxation with no influence on LV contractility regardless of infused doses. On the other hand, high dose of ANP decreased ESP, EDP and EA, and increased SV, reflecting systolic effects in this dose.

1049-158 Results of an Open Label Dose Response Study of Thalidomide in Patients With Advanced Heart Failure and Elevated Levels of TNF
Blyksem Bozkuiz, Adrienne Chee, Doryell Lee-Jackson, Anita Deswal, Jerome B. Zeldis, Douglas L. Mann. Baylor College of Medicine, Houston, TX; Cajeane Corporation, Warren, NJ, USA

Background: Recent studies suggest that inhibition of TNF (Tumor Necrosis Factor) in chronic heart failure (HF) can result in suppression of left ventricular proarrhythmic is summarized in the table below:

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<tr>
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<th>Dobutamine</th>
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<tr>
<td>Valvul-Yes</td>
<td>17 (23%)</td>
<td>3 (4%)</td>
<td>&lt;0.001</td>
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<tr>
<td>No</td>
<td>10 (77%)</td>
<td>12 (95%)</td>
<td>0.019</td>
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<tr>
<td>CAPS-Yes</td>
<td>7 (10%)</td>
<td>0 (0%)</td>
<td>0.001</td>
</tr>
<tr>
<td>No</td>
<td>65 (90%)</td>
<td>80 (100%)</td>
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At 24 hours, mean systolic blood pressure was decreased by 12 and 13 mm Hg in the 2 nesiritide dose groups, respectively, and was decreased by 1 mm Hg in the dobutamine group. (p-value is <0.001)

Conclusions: Nesiritide, a new intravenous therapy for dCHF, was not proarrhythmic in this study, whereas dobutamine was associated with significant proarrhythmia.

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Roles of Apoptosis and Cytokine Families on the Reperfusion Injury in the Patient With Acute Myocardial Infarction

Elchi Gashi, Akihiko Nomoto, Hikko Haru, Toshiaki Kastegi
Third Department of Internal Medicine, Showa University School of Medicine
Tokyo, Japan

Background: The roles of apoptosis and cytokines on the mechanism of reperfusion injury after PTCA have been still controversial. Recently, Fas/Fas-L system has been established as one of the regulating pathways of the apoptotic cell death. The aim of this study is to clarify roles of Fas/Fas-L system and cytokines in the process of reperfusion injury after PTCA in patients with acute myocardial infarction (MI).

Methods: In the 34 patients with acute anterior MI with successful recanalization by PTCA, blood samples were obtained from coronary sinus (CS) and peripheral vein (PV) at just before and after (0, 15, 24, 48 and 72 hr) recanalization. Plasma concentrations of sFasL, soluble Fas- ligand (apoptosis introducing factor), sFas (soluble Fas; apoptosis inhibiting factor), gp130 (cytokine relating factor), and NMP (nuclear matrix protein; incidence of cell death) were measured by the ELISA and compared with BNP and CKMB activity.

Results: Plasma sFasL concentration of CS indicated 0.092 ng/ml before PTCA, it was transiently increased to 0.16 at 12 hr after PTCA then decreased to 0.092. Those of Pe were lower than CS in all periods and did not indicate significant changes. The sFas concentration of CS indicated 1.02 ng/ml before PTCA. There was no significant change at 12 hr but increased significantly to 1.70 at 24 hr, then gradually decreased. The sFas-L of 12 hr indicated highly correlation with the sFas of 24 hr. Plasma NMP concentration of CS before PTCA was 5.4 U/ml and it was transiently increased to 8.78 at 12 hr, then gradually decreased. Those of Pe were significantly lower than those of CS in all periods. NMP and sFas-L concentrations in CS indicated similar pattern and there was significantly high correlation between them. The gp130 of CS was significantly increased at 12 hr and was higher than that of Pe in all periods. Furthermore peak sFas-L and gp130 indicated highly correlations with both peak CKMB and BNP of 7th day. NMP indicated significant correlation with all cytokines.

Conclusion: We concluded that in MI patients with PTCA apoptosis and cytokine families induced by the reperfusion in the acute stage were strongly related with the infarcted size and cardiac function in the chronic stage.

Determinants of Exercise Tolerance

Sunday, March 12, 2000, 4:00 p.m.–6:00 p.m.
Anaheim Convention Center, Hall A
Presentation Hour: 5:00 p.m.–6:00 p.m.

Distribution of Angiotensin Converting Enzyme Polymorphism is Related With the Level of Physical Performance

Aris Anastasakis, Antigone Miliou, Dimitris Markou, Angeles Rigopoulos, Arntins Theophiloletou, Evangelia Karvouni, Elias Sotydis, Dimos Pantzelos, Eleftherios Dafnis, Pavlos Toutouzas
Department of Cardiology, University of Athens, Greece

Background: Angiotensin converting enzyme (ACE) genotype has been associated with increased physical performance. However, recent data remain controversial, implicating either the II or the DD genotype. In this study we assessed the ACE genotype distribution among elite athletes, middle aged athletes, and control subjects.

Methods: ACE genotype distribution was compared among 48 elite athletes (Group A; 16 male, mean age 22.2 ± 10.5 years), 256 college athletes (Group B; 243 male, mean age 20 ± 5 years) and 100 healthy volunteers from the general population (Group C; 53 male, mean age 36.6 ± 20 years). Group A consisted of 30 weight lifters, 5 medium- and long-distance runners, and 5 rowers. DNA was extracted from peripheral blood samples and ACE genotype (ID, III) was determined using a three-primer polymerase chain reaction amplification.

Results:

<table>
<thead>
<tr>
<th>ACE genotype</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>22 (45.8%)</td>
<td>200 (78.4%)</td>
<td>94 (94.0%)</td>
</tr>
<tr>
<td>ID</td>
<td>16 (31.2%)</td>
<td>32 (12.5%)</td>
<td>6 (6.0%)</td>
</tr>
<tr>
<td>Total</td>
<td>40 (100%)</td>
<td>232 (100%)</td>
<td>100 (100%)</td>
</tr>
</tbody>
</table>

Conclusion: Higher doses of thalidomide suppressed TNF levels in patients with advanced heart failure. Moreover, this was accompanied by improvement in LVEF. These results suggest a larger randomized placebo controlled study with thalidomide or its analogue with a lesser toxicity profile may be warranted.

Epinephrine Induces Free Radical Release and Upregulates Endogenous Superoxide Dismutase Gene and Protein Expression in Human Coronary Artery Endothelial Cells

Jawahar L. Mehta, Francesco Romeo, Dayuan Li, Min Shi
University of Florida and VA Medical Center, Gainesville, FL, USA, University of Rome “For Vergata”, Rome, Italy

Background: Several studies have shown that exercise is an antioxidant stress, and yet it protects ischemia from myocardial damage. A previous study from our group has shown that moderate exercise immediately increases lipid peroxidation, but soon thereafter causes a sustained increase in antioxidant activity in serum (Am J Cardiol 80: 1640–1642, 1997). Since there is a positive correlation between antioxidant production and cardiac events, we designed this study to examine the effect of catecholamines on free radical release and endogenous superoxide dismutase gene and protein expression in human coronary artery endothelial cells (HCAECs).

Methods: HCAECs were exposed to epinephrine (0.1 to 10 μM) for 24 hours. Parallel groups of cells were incubated with an intracellular free-radical scavenger Trolox, or the beta-blockers carvedilol and atenolol (each 10 μM).

Results: At 1 hr of incubation with epinephrine, superoxide anion generation increased by 50 ± 5% in the HCAECs. At 24 hrs of incubation, there was approximately 100% increase in MnSOD and CuZnSOD gene (RT-PCR) and proteins (Western analysis). SOD activity, measured as inhibition of pyrogallol oxidation, was also increased (109 ± 9%). Trolox and the beta-blockers carvedilol and atenolol superoxide anion generation decreased (P < 0.01 vs. epinephrine alone). The upregulation of SOD was also blocked by pre-treatment of HCAECs with Trolox. Treatment of cells with different beta-blockers carvedilol and atenolol also blocked the upregulation of SOD (P < 0.01 vs. epinephrine).

Conclusion: These observations show that epinephrine via beta-adrenoreceptor activation causes free radical generation, but at 24 hrs it causes a marked increase in endogenous antioxidant species. These observations may be the basis of long-term benefits of exercise.

Intervenous Testosterone has no Effect on Cardiovascular and Ventilatory Responses to Exercise in Elderly Men With Coronary Artery Disease

Niall M. Moyna, Alan W. Ahlborg, C. Michaela White, M. Ferraro-Borgida, Carol C. McGill, Gary V. Heaver, Rehan Qayyum, Paul T. Thompson
Hartford Hospital, Hartford, CT, USA

Background: Data suggest that the acute IV administration of physiologic doses of testosterone alters the ischemic threshold in men with coronary artery disease (CAD). However, the effects of acute administration of physiologic and supraphysiologic doses of testosterone on cardiovascular and ventilatory responses to exercise are unknown.

Methods: Seventeen men (65 ± 5 yr) with stable CAD, and evidence of exercise induced ischemia on radionucleotide imaging received intravenous testosterone or placebo in double-blind randomized order prior to undertaking a treadmill exercise test (Bruce protocol). The testosterone dose was individualized to double (physiologic) or increase to 6 times (supraphysiologic) baseline serum testosterone levels, based upon our previous pharmacokinetic study (J Clin Pharmacol, 3 (3) 792–97, 1998). Cardiovascular and ventilatory measures were compared at the anaerobic threshold (AT) and peak exercise.

Results: Acute administration of physiologic or supraphysiologic IV testosterone had no effect on HR (heart rate), VO₂ (oxygen uptake), Ve (minute ventilation) or R (respiratory exchange ratio) at the AT (Table 1) or total exercise time, HR, VO₂, Ve, R, BP (rate pressure product) and RPE (rating of perceived exertion) at peak exercise. (Table 2)
The skeletal muscle intrinsic mitochondrial oxidative capacity to determine the exercise capacity in normal subjects.

Methods: SM Vastus Lateralis biopsies have been obtained from 7 sedentary normals (SED, mVO2 < 100% of predicted), 7 physically active normals (VO2max > 60 ml/kg/min), 7 patients with chronic heart failure (CHF), and 7 patients with ischemic heart disease (IHD). Chronotropic Assessment Exercise Protocol (CAEP) was performed in all patients. heart rate, blood pressure, and oxygen uptake were recorded during the CAEP. The exercise intensity was calculated using the Karvonen equation.

Results: Values are expressed in table as means ± SEM, p < 0.05.

<table>
<thead>
<tr>
<th>Method</th>
<th>Value (SED)</th>
<th>Value (VO2max)</th>
<th>Value (CHF)</th>
<th>Value (IHD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO2 max (ml/kg/min)</td>
<td>45.2 ± 5.3</td>
<td>50.8 ± 4.2</td>
<td>32.4 ± 4.8</td>
<td>45.2 ± 5.3</td>
</tr>
<tr>
<td>%VO2max</td>
<td>95.2 ± 2.3</td>
<td>91.6 ± 3.5</td>
<td>85.2 ± 3.8</td>
<td>93.2 ± 2.9</td>
</tr>
<tr>
<td>VE (l/min)</td>
<td>45.2 ± 6.3</td>
<td>50.8 ± 4.2</td>
<td>32.4 ± 4.8</td>
<td>45.2 ± 5.3</td>
</tr>
<tr>
<td>RER</td>
<td>0.75 ± 0.05</td>
<td>0.78 ± 0.08</td>
<td>0.76 ± 0.05</td>
<td>0.75 ± 0.05</td>
</tr>
</tbody>
</table>

Conclusions: The VO2 max and %VO2max are lower in patients with CHF and IHD compared to sedentary normals and physically active normals. The VE and RER are similar in all groups. The CAEP is a useful tool to assess the exercise capacity in patients with heart failure.
Cytokines and Endothelial Changes in Myocardial Failure

Monday, March 13, 2000, 9:00 a.m.—11:00 a.m.
Anaheim Convention Center, Hall A
Presentation Hour: 10:00 a.m.—11:00 a.m.

**1071 - Cytokines and Endothelial Changes in Myocardial Failure**

**Background:** Increased levels of TNF-a seen in chronic heart failure (CHF) have been shown to depress myocardial function. ACE inhibitors (ACE-I) and AT1 blockers (AT1-B) are beneficial in CHF.

**Methods:** We studied the effects of ACE-I (Enalapril) and AT1-B (Can- desartan) on TNF-a production in the remote non-infarcted myocardium (NIM) of 6 week post MI rats and corresponding areas of sham operated rats. We also investigated whether this TNF-a production affects myocyte contractile function in this region, Infarcted rats were treated with either water, ACE-I (1 mg/kg), AT1-B (10 mg/kg) or combination in drinking water. Treatment was started within 24 h after MI and continued for 6 weeks, when rats were sacrificed.

**Results:** MI hearts were significantly remodeled and dysfunctional. Both ACE-I and AT1-B inhibitors improved LV function (table). TNF-a levels were undetectable in sham myocardium but increased in water treated MI hearts (0.94 ± 0.08 pg/ml). AT1-B alone-reduced TNF-a production in MI hearts (0.63 ± 0.03 pg/ml) where as ACE-I alone did not (0.81 ± 0.03 pg/ml). In contrast, ACE-I in combination with AT1-B had a marked effect on TNF-a production (0.41 ± 0.01 pg/ml). However the contractile function of LV myocytes in response to serial doses of (CaCl2) was not different in all the groups.

**Conclusion:** These data suggest that elevated levels of TNF-a seen in 6 week post MI, globally dysfunctional hearts, do not affect isolated myocyte contractile function. The role of TNF-a in global LV dysfunction is unclear. The mechanism and implication of these findings need to be clarified.

**1071-142 - Effect of ACE Inhibitor and AT1 Blocker on Myocardial Expression of TNF-a in Post MI Ventricular Remodeling**

Sudhir Gupta, Arun J.C. Prakash,inder S. Anand. Division of Cardiology, VA Medical Center and University of Minnesota, Minneapolis, MN-55417, USA

**Background:** Myocardial failure rat model we have studied the effect of carvedilol (C) on myocardial collagen and fibrogenic cytokine expression which is important for compliance and the process of remodeling. In an experimental post MI heart failure rat model we have studied the effect of carvedilol (C) on myocardial collagen type I and III, transforming growth factor (TGF-β) and tumor necrosis factor (TNF) gene expression.

**Methods:** Using the rat model of MI induced by coronary ligation, myocardial mRNA levels for collagen I, III, TGF-β, and TNF were evaluated in the non-infarcted myocardium (NIM) and infarcted areas by quantitative competitive reverse transcriptase PCR (MIMIC fragment technique) after 11 weeks oral therapy with C and compared to untreated ligated animals and sham operated.

**Results:** In the NIM, C therapy was associated with a significant reduction (18-fold) of collagen mRNAs levels (p = 0.004), but unchanged collagen mRNA levels and therefore a reduced collagen/βIIa ratio compared to untreated NIM. There were no significant changes in TGF-β or TNF levels in the NIM compared to sham. In the infarcted area there were highly significant increases in collagen I, III, TGF-β and TNF mRNA levels (all p < 0.001) but these were unaffected by C therapy.

**Conclusions:** C therapy is associated with a significant reduction of type I collagen in the non-infarcted myocardium which may have an important impact on compliance. This action of C appears to be independent of both TGF-β and TNF.

Effect of Adrenergic Blockade on Myocardial Collagen Type III Ratio and Cytokine Expression Post Myocardial Infarction

Shan Wei, Ka B. Lai, Louis T.C. Chow, John E. Sanderson. Division of Cardiology, The Chinese University of Hong Kong, China

**Background:** β-adrenergic blockade reduces mortality post myocardial infarction (MI) and in heart failure but there is little information on its effect on myocardial collagen and fibrogenic cytokine expression which is important for compliance and the process of remodeling. In an experimental post MI heart failure rat model we have studied the effect of carvedilol (C) on myocardial collagen type I and III, transforming growth factor (TGF-β) and tumor necrosis factor (TNF) gene expression.

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Neurohumoral Response During Exercise in Healthy Controls and Patients With Chronic Heart Failure

Mohammed Yousufuddin, Waqar Shamim, Michael Henein, Fouad R. Amin, Stefan D. Anker, Michael Kemp, A. Hopfer, Andrew J.S. Coutts. National Heart and Lung Institute and Royal Brompton Hospital, London, UK

**Background:** Interaction between the autonomic nervous system and the heart and peripheral vessels may play an important role in determining exercise capacity. The response of various neurohumoral factors during exercise in patients with CHF may be different from normals.

**Methods:** We measured plasma concentrations of noradrenaline (NE), as a measure of sympathetic nervous system activity, atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), both of which indirectly reflect cardiac hemodynamics in CHF, and endorphin/β-endorphin (endorphin-β) (one of the measures of endothelial dysfunction) in 10 healthy controls (37 ± 14 yr) and 29 patients (51 ± 15 yr) with stable CHF (LVEF 31 ± 15%) after 30 min supine rest and immediately after maximal treadmill exercise in 12 h post-absorptive state.

**Results:** Peak oxygen consumption was higher in controls compared to patients (33.7 ± 7 vs 20.8 ± 6 ml/kg/min; p < 0.001). Resting values for NE, ANP, BNP, and ET-1 were all positively correlated with those of the postexercise values in both controls and patients with correlation coefficients between 0.72 to 0.98 and p values between 0.02 to <0.0001. Exercise induced increase in NE level was higher in normals compared to patients (128 ± 96 vs 59 ± 45%; p = 0.008). Increase in plasma ET-1 level was greater in patients than controls (47 ± 26 vs 20 ± 18%; p = 0.01). There was no difference between two groups with regard to exercise induced percent change in plasma concentrations of ANP and BNP. Preexercise resting plasma ET-1 was positively correlated with both preexercise and post exercise plasma levels of ANP [pre (p = 0.01) post (p = 0.001)] and BNP [pre (p = 0.005)] post (p = 0.006) in patients but not in controls.

**Conclusion:** Of all the neurohumoral factors studied, NE in controls and ET-1 in patients showed a greater percent increase with exercise indicating potentially greater importance of ET-1 to the exercise pathophysiology in CHF.
1071-145  Clinical Assessment of Myocardial Dysfunction in Targeted Expression of MCP-1 in the Murine Heart

Michael F. Deucher, Pappachan E, Kolattukudy, Doug M. Brown, Patricia Sanitle Hatton, Philip F. Binkley. Ohio State Medical Center, Columbus, OH, USA

Targeted expression of MCP-1 in the murine myocardium chemotactically recruits monocytes causing a severe cardiomyopathy highlighted by mononuclear infiltrates, myocyte hypertrophy, interstitial edema, and fibrosis. The purpose of this study is to characterize the functional cardiac changes in this model over time.

Methods: Studies were performed in mice with targeted expression of MCP-1 and age-matched, littermate controls. The unanesthetized and induced echocardiography were performed on anesthetized mice and continuous ECG monitoring units were implanted intraoperatively. ECG signals were continuously recorded on PM tape and digitized using WinDax. A DP B200 Analyzer recorded BP measurements.

Results: By ECHO, heterozygous transgenic mice had substantial left ventricular hypertrophy and dilatation. LV mass was 21% greater with both systolic and diastolic left ventricular internal diameters increased. Fractional shortening (FS) showed dramatic reduction with first-generation transgenics having a value of 37% and controls 64%. Subsequent generations of these heterozygous mice and homozygous mice were both found to have more severe reduction in ventricular function. At two months, homozygotes had a FS of 30% and by six months the second-generation heterozygotes were found to have a FS of 15%. ECG monitoring in the heterozygotes showed the QRS complex progressively lengthened from 6-9 months, the JT interval abruptly increased at 6 months, and the QT interval gradually prolonged from 6-9 months. In heterozygotes, the average systolic BP was 12% greater than the control mice, and a nonsignificant trend toward higher readings were observed in the younger transgenics.

Conclusions: Targeted expression of MCP-1 in murine myocardium initiates a progressive cardiomyopathic process resulting in left ventricular hypertrophy and dilatation, lengthening of the QRS complex, JT and QT intervals, and mild elevation in systolic BP.

1071-146  U-74 Inhibits the Cytokine Induced iNOS Expression Via Elevation of IKB and Depression of NF-B in Cultured Endothelial Cells

Ronald J. M. B, Ronshaas, M., Maylam M. T, Hill, Pieter A. Drawdeman, Rien van der Zee. Dept. of Cardiology, Cardiovascular Research Institute Maastricht; RUG Hospital, Delft, The Netherlands

Introduction: Myocardial NO production is increased in patients with heart failure, due to increased inducible NOS (iNOS) expression. NO high levels lead to myocardial injury and reduced contractility. Cytokines like interleukin-1 beta (IL-1β) are able to activate the iNOS gene. Potentially, selective inhibition of iNOS activity could preserve cardiac function. U-74, a 21-aminoacid-lazaroid inhibits the transcription of cytokine induced iNOS but not eNOS in cultured endothelial cells. In the present study, we tested the hypothesis that U-74 increases the expression of IKB and depresses the expression of NF-B which potentially can inhibit the iNOS transcription.

Methods: Cells were cultured in phenol-red free medium and treated with 5 pg/mL IL-1β in the absence or presence of U-74 (10⁻³ M). 60 minutes after cytokine stimulation total protein was isolated. NO release was measured via the Griess assay. The expression of iNOS at the RNA and protein level was studied by RT-PCR and Western analysis. In identical experiments, the expression of IKB and NF-B was assessed via Western analysis.

Results: A rise in NO release up to 80 μM/m² was detected 40 minutes after addition of IL-1β. This rise could be blocked completely by adding U-74 amunetherenate. U-74 alone did not influence baseline NO production. Western analysis revealed that U-74 did not influence eNOS protein levels, but a marked reduction of cytokine induced iNOS expression was found. RT-PCR showed that U-74 inhibited the transcription of the iNOS gene completely. Detection of either IKB or NF-B showed a marked U-74 dependent increase in IKB (2.5×) and a depression of NF-B (2×).

Conclusion: U-74, a 21-aminoacid-lazaroid inhibits the transcription of cytokine induced iNOS but not eNOS in cultured endothelial cells. The mechanism involves elevation of IKB protein and a marked down-regulation of NF-B mediated via U-74.

1071-147  Myocardial Dysregulation of Chemokines and Their Receptors in Human End-Stage Heart Failure

Jahi K. Darnell, Hans-O. Eiken, Erik Ora, Vigdis Bjørvoll, Arne Yndestad, Thor Ulstein, Geir Christensen, Thris Tennesen, Håkon Hallbackam, Odd R. Geirán, Halfdan Aas, Svein Simonsen, Stig S. Freland, Lars Gulsetad, Pål Aukrust. The National Hospital, University of Oslo, Oslo, Norway

Background: Persistent immune activation has recently been implicated in the pathogenesis of congestive heart failure (CHF). Chemokines are essential for the recruitment and activation of leukocytes from the circulation into inflamed tissue, and recent studies suggest that chemokines also may be important mediators of several other biological processes such as collagen turnover, angiogenesis and apoptosis. We have hypothesized a pathogenic role for chemokines in the development of CHF, and in the present study we examined the myocardial gene expression and cellular localization of chemokines and their corresponding receptors in human end-stage heart failure.

Methods: We examined mRNA levels of 23 different chemokine and chemokine receptor genes in explanted hearts from 11 patients with end-stage heart failure (all chambers) and in 10 organ donors (left ventricle [n = 6] and atrium [n = 6]) using RNase protection assays. By immunohistochemical techniques we examined the localization of the chemokines and chemokine receptors with the highest mRNA expression.

Results: Several findings were revealed: (i) 8 chemokine and 9 chemokine receptor genes were expressed in both chronic failing and nonfailing myocardium. (ii) Particular high mRNA levels were found for monocyte chemotactic protein (MCP)-1, interleukin-8 (IL-8) and the chemokine receptor, CXCR4 in both chronic failing and nonfailing myocardium. (iii) In the chemokine deficient myocardium left atria expressed elevated chemokine mRNA levels compared to left ventricles (p < 0.001). (iv) Chronic failing left ventricles and left atria expressed decreased chemokine (e.g., MCP-1, p < 0.01) and increased chemokine receptor (e.g., CXCR4, p < 0.01) mRNA levels compared to corresponding chambers in the nonfailing hearts. (v) The chemokines MCP-1 and IL-8 and the chemokine receptor CXCR4 were immunolocalized to the cardiomyocytes.

Conclusions: This first demonstration of myocardial chemokine and chemokine receptor expression may point to family of previously unrecognized mediators present in the human myocardium, possibly involved in the pathogenesis of CHF.

1071-148  The Positive Inotropic Effects of Hydrostatic Pressure are Buffered by the Endocardial Endothelium Via Prostaglandins

Christopher J. Zeitz, Stanislas U. Syrs, Dirk L. Brutsaert. Department of Physiology and Medicine, University of Antwerp, Belgium

Background: Despite evidence of mechano-sensitive pathways in endocardial endothelium (EE), an effect of increased hydrostatic pressure (P) on myocardial contractile function has not been demonstrated. We have subjected isolated cardiac papillary muscles to hydrostatic pressure, followed by its removal and examined the impact on contractile indices.

Methods: Rabbit right ventricular papillary muscles (n = 68; ox KR; 0.6 Hz) were either immediately stabilized under P for at least 2 hrs or stabilized at atmospheric pressure for 2 hrs with subsequent addition of P. When required, the EE was removed with 5% Tripton. Following stabilization, P was either added (+P) or removed (−P), depending on the stabilization state, with subsequent monitoring for 40 minutes, using paired control muscles. The impact of 10 μM L-NMMA (n = 6), 10 μM Indomethacin (Indo) (n = 6) or 1 μM BQ-23 (n = 6) on the response to −P and +P was also examined versus control muscles (n = 6) subjected to the same P protocol.

Results: The Positive Inotropic Effects of Hydrostatic Pressure are Buffered by the Endocardial Endothelium Via Prostaglandins.

<table>
<thead>
<tr>
<th>Active Tension</th>
<th>Time 1/2 Relaxation</th>
<th>Peak Shortening</th>
</tr>
</thead>
<tbody>
<tr>
<td>-P&lt;sub&gt;EE&lt;/sub&gt; (n = 7)</td>
<td>2.5 ± 3.7</td>
<td>2.2 ± 1.2</td>
</tr>
<tr>
<td>+P&lt;sub&gt;EE&lt;/sub&gt; (n = 8)</td>
<td>6.6 ± 2.8</td>
<td>2.5 ± 0.6</td>
</tr>
<tr>
<td>-P&lt;sub&gt;EE&lt;/sub&gt; (n = 7)</td>
<td>3.2 ± 4.7</td>
<td>1.4 ± 0.3</td>
</tr>
<tr>
<td>+P&lt;sub&gt;EE&lt;/sub&gt; (n = 8)</td>
<td>13.2 ± 5.2</td>
<td>3.2 ± 1.0</td>
</tr>
<tr>
<td>-P&lt;sub&gt;EE-NNMMA&lt;/sub&gt;</td>
<td>5.2 ± 3.5</td>
<td>-1.5 ± 1.0</td>
</tr>
<tr>
<td>+P&lt;sub&gt;EE-NNMMA&lt;/sub&gt;</td>
<td>2.1 ± 3.6</td>
<td>3.3 ± 1.2</td>
</tr>
<tr>
<td>-P&lt;sub&gt;EE&lt;/sub&gt;&lt;sub&gt;-Indo&lt;/sub&gt;</td>
<td>16.2 ± 9.8</td>
<td>-4.1 ± 1.6</td>
</tr>
<tr>
<td>+P&lt;sub&gt;EE&lt;/sub&gt;&lt;sub&gt;-Indo&lt;/sub&gt;</td>
<td>12.4 ± 7.3</td>
<td>2.4 ± 1.3</td>
</tr>
<tr>
<td>-P&lt;sub&gt;EE&lt;/sub&gt;&lt;sub&gt;-BQ-23&lt;/sub&gt;</td>
<td>1.7 ± 0.6</td>
<td>-4.4 ± 1.1</td>
</tr>
<tr>
<td>+P&lt;sub&gt;EE&lt;/sub&gt;&lt;sub&gt;-BQ-23&lt;/sub&gt;</td>
<td>5.8 ± 7.3</td>
<td>6.7 ± 3.8</td>
</tr>
</tbody>
</table>

*p = 0.05 on repeated measures ANOVA vs control muscle groups.

Addition of P resulted in a positive inotropic effect that was virtually abolished in the presence of EE. Effects of +P and −P were maximal when...
prostaglandin synthesis was blocked by Indo. P effects on time to half relaxation (tHR) appear largely independent of EE and pharmacology.

Conclusions: This is the first demonstration that contractile function of cardiac muscle is directly modulated by P. The "buffering" effect of the EE is apparent function may be an important predictor of maximal exercise capacity in normal individuals and patients with heart failure.

Methods: Endothelium-dependent (flow) and independent (GTN) vascular responses in the brachial artery were assessed by high-resolution ultrasound in 8 volunteers (age 39.7 ± 14 yrs) and 18 patients (age 51.0 ±12 yrs) with CHF. Peak oxygen consumption (MV02) was measured by radionuclide ventriculography in patients.

Results: The flow-mediated (10.93 ± 3.94% vs 2.17 ± 1.12%; p = 0.0001), GTN-induced (16.10 ± 5.9% vs. 7.65 ± 3.8%; p = 0.01) percentage dilatations and MV02 (31 ± 12 vs 7 ± 5 ml/min/l00 ml; p = 0.05), peak hyperaemic flow (45.5 ± 15 vs 92 ± 27 ml/min/100 ml; p = 0.05) or total flow over 5 min of reactive hyperaemia (68 ± 2 ml vs. 69 ± 27; p = 0.68). MV02 was closely related to flow-mediated dilatation (r = 0.72; p < 0.0001) but not to GTN-mediated dilatation (r = 0.37; p = 0.0002) nor to blood flows (r = 0.22; p = 0.23). There was no relation between flow-mediated dilatation (r = 0.72; p < 0.0001) but not to GTN-mediated dilatation (r = 0.37; p = 0.0002) and MV02 (r = 0.47; p = 0.05) in patients.

Conclusion: The strong relation between flow-dependent endothelium-mediated vascular response and MV02 suggests that the vascular endothelial function may be an important predictor of maximal exercise capacity in normal individuals and patients with heart failure.

1071-149

Endothelium Dependent and Independent Vascular Responses and Blood Flow in the Brachial Artery of Healthy Controls and Patients With Chronic Heart Failure (CHF): Relationship to Peak Oxygen Consumption and Left Ventricular Ejection Fraction

Mohammed Yousufuddin, Waqar Shami, Jonathan S. Chamber, Fouad R. Amin, Stefan D. Anker, Andrew J.S. Coats. National Heart and Lung Institute and Royal Brompton Hospital, London, UK

Background: Endothelial function may be of relevance in the pathophysiology of exercise tolerance in healthy controls and patients with CHF.

Methods: Endothelium-dependent (flow) and independent (GTN) vascular responses in the brachial artery were assessed by high-resolution ultrasound imaging in 8 volunteers (age 41.2 ± 12 yr) and 21 patients (age 59.6 ± 12 yr) with CHF. Peak oxygen consumption (MV02) was measured by radionuclide ventriculography in patients.

Results: The flow-mediated dilatation (10.93 ± 3.94% vs 2.17 ± 1.12%; p = 0.0001), GTN-induced (16.10 ± 5.9% vs. 7.65 ± 3.8%; p = 0.01) percentage dilatations and MV02 (31 ± 12 vs 7 ± 5 ml/min/100 ml; p = 0.05), peak hyperaemic flow (45.5 ± 15 vs 92 ± 27 ml/min/100 ml; p = 0.05) or total flow over 5 min of reactive hyperaemia (68 ± 2 ml vs. 69 ± 27; p = 0.68). MV02 was closely related to flow-mediated dilatation (r = 0.72; p < 0.0001) but not to GTN-mediated dilatation (r = 0.37; p = 0.0002) nor to blood flows (r = 0.22; p = 0.23). There was no relation between flow-mediated dilatation and MV02 in patients.

Conclusion: The strong relation between flow-dependent endothelium-mediated vascular response and MV02 suggests that the vascular endothelial function may be an important predictor of maximal exercise capacity in normal individuals and patients with heart failure.

1071-150

Non-invasive Assessment of Exercise Induced Alterations of the Conduit Artery Tone in Healthy Controls and Patients With Chronic Heart Failure (CHF): Relationship to Endothelin-1 and Nor-EPinephrine

Mohammed Yousufuddin, Waqar Shami, Jonathan S. Chamber, Michael Y. Henein, Fouad R. Amin, Stefan D. Anker, Michael Kemp, J. Hooper, Andrew J.S. Coats. National Heart and Lung Institute and Royal Brompton Hospital, London, UK

Background: This study is aimed at determining alterations in brachial artery diameter and blood flow before and after exercise in 8 healthy volunteers (age 39.7 ± 14 yrs) and 18 patients (age 51.0 ± 12 yrs) with chronic heart failure (CHF).

Methods: Data from the UNC Heart Failure Database was analyzed in 680 patients (pts) who were 44% African-American (AA) and 31% female who had symptomatic heart failure (NYHA class 2.8 ± 0.8, mean ± SD) with reduced left ventricular ejection fraction (LVEF) of 25 ± 13 and a body mass (Bmass) of 27 ± 7.3. Data on vital status was available in 97% of these patients with mean length of follow-up 1.9 ± 2.1 years.

Results: AA were more likely to have hypertension (67 vs. 38%), be female (37 vs 26%), and have causes other than ischemic heart disease as their primary etiology of heart failure (14% vs 45%) than other races (all p < 0.01). LVEF (26 ± 14 versus 26 ± 12) and NYHA class (2.8 ± 0.7 vs 2.9 ± 0.7) were similar between AA and other races (all p > 0.1). Body mass was greater in AA than in other races (28.2 ± 8.6 vs 26.4 ± 6.1) and baseline systolic blood pressure was higher (124 ± 23 vs 116 ± 19 mmHg), both p < 0.01. (Unadjusted analysis suggested better survival in AA versus other races (relative risk 0.76, 95% CI 0.590-0.977, p = 0.032). Adjusted analysis taking into account characteristics previously shown to be of prognostic importance in our database (LVEF, age, gender, etiology, NYHA Class) and other differences in baseline characteristics found no difference in survival between AA and other races (relative risk (1.097 95% CI 0.830-1.451, p = 0.514).

Conclusion: Although baseline clinical characteristics differed between AA and other races, adjusted analysis taking these differences and other prognostic factors into account found similar survival rates between AA and other races.

1072

Diagnosis and Prognosis in Heart Failure I

Monday, March 13, 2000, 9:00 a.m.—11:00 a.m.
Anahiem Convention Center, Hall A
Presentation Hour: 10:00 a.m.—11:00 a.m.

1072-152

Survival Rates are Similar Between African-Americans and Other Races With Heart Failure

Stephanie H. Dunlap, Carlos A. Sueta, Todd A. Schwartz, Taaseneem Islam, Koran Webster, Kirkwood F. Adams Jr., University of North Carolina, Chapel Hill, NO, USA

Background: Baseline clinical characteristics are known to differ between African-Americans (AA) and other races with heart failure, suggesting mortality rates may differ as well. We investigated the association between race and survival in patients (pts) with heart failure.

Methods: Data from the UNC Heart Failure Database was analyzed in 680 patients (pts) who were 44% African-American (AA) and 31% female who had symptomatic heart failure (NYHA class 2.8 ± 0.8, mean ± SD) with reduced left ventricular ejection fraction (LVEF) of 26 ± 19 and a body mass (Bmass) of 27 ± 7.3. Data on vital status was available in 97% of these patients with mean length of follow-up 1.9 ± 2.1 years.

Results: AA were more likely to have hypertension (67 vs. 38%), be female (37 vs 26%), and have causes other than ischemic heart disease as their primary etiology of heart failure (14% vs 45%) than other races (all p < 0.01). LVEF (26 ± 14 versus 26 ± 12) and NYHA class (2.8 ± 0.7 vs 2.9 ± 0.7) were similar between AA and other races (all p > 0.1). Body mass was greater in AA than in other races (28.2 ± 8.6 vs 26.4 ± 6.1) and baseline systolic blood pressure was higher (124 ± 23 vs 116 ± 19 mmHg), both p < 0.01. (Unadjusted analysis suggested better survival in AA versus other races (relative risk 0.76, 95% CI 0.590-0.977, p = 0.032). Adjusted analysis taking into account characteristics previously shown to be of prognostic importance in our database (LVEF, age, gender, etiology, NYHA Class) and other differences in baseline characteristics found no difference in survival between AA and other races (relative risk (1.097 95% CI 0.830-1.451, p = 0.514).

Conclusion: Although baseline clinical characteristics differed between AA and other races, adjusted analysis taking these differences and other prognostic factors into account found similar survival rates between AA and other races.
Depression in Heart Failure: Clinical Characteristics and Impact on Outcomes

Christopher M. O'Connor, Wei Jiang, Jude Alexandra, Eric Christopher, Maggie Kuchibhatla, Chad Davenport, Christopher Simoner, Ranga R. Krishnan. Duke University Medical Center, Durham, North Carolina, USA

Background: Previous studies have indicated that patients with ischemic heart disease, suffer a high rate of depression which is associated with increased morbidity and mortality. However, such a relationship has not been studied thoroughly in patients with heart failure (HF). The purpose of this study was to examine the prevalence and clinical characteristics of depression in patients with HF and its impact on mortality.

Methods: 374 consecutive patients hospitalized with a clinical diagnosis of HF with a left ventricular ejection fraction below 35% were approached for the study from April 1997 to June 1998. 357 patients consented for participation. The patients were first given the Beck Depression Inventory (BDI), then underwent Diagnostic Interview Schedule (DIS) if the BDI score was > 10. The median age of the cohort was 65 years, 37% were female, 30% were minority, and 55% had ischemic etiology.

Results: 19.4% of patients had a BDI score > 10 indicative of minor depression and 14% were DIS positive suggestive of major depression. The short and long-term mortality rates are shown below.

<table>
<thead>
<tr>
<th>Scale</th>
<th>3 month mortality (%)</th>
<th>P value</th>
<th>12 month mortality (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI ≤ 10</td>
<td>4.6</td>
<td>0.006</td>
<td>22.0</td>
<td>0.02</td>
</tr>
<tr>
<td>BDI &gt; 10</td>
<td>5.9</td>
<td>0.11</td>
<td>27.2</td>
<td>0.006</td>
</tr>
<tr>
<td>DIS</td>
<td>15.9</td>
<td>0.008</td>
<td>27.2</td>
<td>0.006</td>
</tr>
<tr>
<td>DIS &gt; 2</td>
<td>6.7</td>
<td>0.11</td>
<td>27.2</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Conclusion: HF patients have a high prevalence of minor and major depression which is associated with a greater than 2 times higher rate of mortality at 3 months and 12 months than HF patients who are not depressed.

Prognostic Significance of Left Bundle Branch Block in a Cohort of 8931 Patients With Different Levels of LV Systolic Function

Stram Padmanabhan, Jatin Amin, Helme Silvet, Ramdas G. Pai. Loma Linda VA Medical Center, Loma Linda, CA, USA

Left bundle branch block (LBBB) is uncommon as a benign abnormality. However, whether it has any impact on mortality in those with normal LV performance and in those with various degrees of LV dysfunction is not known. We investigated the prognostic significance of LBBB in 8,931 patients undergoing echocardiography, 5,130 of whom had normal LV systolic function (age 66 ± 13 years, LVEF > 55%). LBBB was present in 385 patients and there were 1,911 deaths over a mean follow up of 913 days.

Results: The prevalence of LBBB increased with diminishing LV function; being 1.2% in patients with normal LV function (EF > 55%), 4.5% in those with mild LV dysfunction (EF 41–54%), 10% in those with moderate LV dysfunction (EF 31–40%) and 10% in those with severe LV dysfunction (EF < 30%). Other correlates of LBBB includes greater age (p < 0.0001), larger LV size (p < 0.0001), presence of atrial fibrillation (p < 0.001), presence of inferior but not anterior myocardial infarction on the electrocardiogram (p < 0.0001), presence of greater degrees of mitral and tricuspid regurgitation (p < 0.0001) and greater dimensions of all cardiac chambers (p < 0.0001). The 7 year mortality was 52% in those with RBBB compared to 37% in those with normal LV function and patients with mild or moderate LV dysfunction.

Conclusions: (1) The prevalence of RBBB increases minimally with diminishing LV systolic function, but is strongly associated with age, cardiac chamber size and valvular disease. (2) There is an increase in mortality with the presence of RBBB in those with normal LV function and patients with mild or moderate LV dysfunction. (3) The effect of RBBB on mortality is least pronounced in those with severe LV dysfunction.

Prognostic Significance of Right Bundle Branch Block in a Cohort of 8931 Patients With Different Levels of LV Systolic Function

Helme Silvet, Jatin Amin, Sriram Padmanabhan, Ramdas G. Pai, Loma Linda VA Medical Center, Loma Linda, CA, USA

Right bundle branch block (RBBB) is present in 1% of normal individuals and is thought to be a benign abnormality. We investigated the prognostic significance of RBBB as function of the level of LV systolic function in 8,931 patients undergoing echocardiography (age 66 ± 13 years, EF 51 ± 15%). 5130 patients with normal systolic function. RBBB was present in 693 patients and there were 1,911 deaths over a mean follow up of 913 days.

Results: The prevalence of RBBB increased only minimally with diminishing LV function; being 7% in patients with normal LV function (EF > 55%), 8% in those with mild LV dysfunction (EF 41–54%), 10% in those with moderate LV dysfunction (EF 31–40%) and 10% in those with severe LV dysfunction (EF < 30%). Other correlates of RBBB includes greater age (p < 0.0001), larger LV size (p < 0.0001), presence of atrial fibrillation (p < 0.001), presence of inferior but not anterior myocardial infarction on the electrocardiogram (p < 0.0001), presence of greater degrees of mitral and tricuspid regurgitation (p < 0.0001) and greater dimensions of all cardiac chambers (p < 0.0001). The 7 year mortality was most pronounced in those with mild (7 year mortality 48 ± 3%, p = 0.005) and moderate LV dysfunction (7 year mortality 72 ± 4%, p = 0.002). Among the various subgroups, the effect of RBBB on mortality was most pronounced in those with normal LV function (7 year mortality 45 vs. 30%, p = 0.03) and those with severe LV dysfunction (7 year mortality 68 vs. 53%, p = ns).

Conclusions: (1) The presence of RBBB increases minimally with diminishing LV systolic function, but is strongly associated with age, cardiac chamber size and valvular disease. (2) There is an increase in mortality with the presence of RBBB in those with normal LV function and patients with mild or moderate LV dysfunction. (3) The effect of RBBB on mortality is least pronounced in those with severe LV dysfunction.

Prognostic Significance of Right Bundle Branch Block in a Cohort of 8931 Patients With Different Levels of LV Systolic Function

Andreas Kikowki, Caroline Bergmeier, Rudolf Schrie, Anseil K. Ott, Ulf Gieseler, Helmut Thomas, Jochem Sanges. For the MITRA-investigators: Department of Cardiology, Herzzentrum Ludwigsheim, Speyer; Bad Duerkheim, Germany

Purpose: The extent of left ventricular dysfunction (LVD) and longterm mortality in nonselected patients (P) with acute myocardial infarction (AMI) after implementation of high rates of acute recanalisation, aspirin, ¿-blockers and ACE-inhibitors was assessed.

Methods: The Southwest German "Maximal Individual Therapy in Acute Myocardial Infarction" (MITRA) - trial is a prospective multicenter observational study of the current treatment of AMI. 4495 consecutive P with AMI were discharged from hospital alive from 5/94 to 1/97. Left ventricular ejection fraction (EF) was evaluated echocardiographically. Acute treatment: 98% recanalisation, 94% aspirine, 53% ¿-blockers, 51% ACE-inhibitors. Mean follow-up time was 16 months.

Results: (1) At discharge 1899 P (42%) had normal EF, 1303 (29%) showed slight, 924 (21%) moderate and 379 (8%) severe reduction of EF. (2) Medication at discharge in P with normal, slightly, moderately and severely reduced EF. ¿-blockers in 68.7%, 65.1%, 51.7% and 35.6% respectively; ACE-inhibitors in 63%, 73%, 80.8% and 62.2% respectively. (3) Longterm mortality (** p < 0.001):

<table>
<thead>
<tr>
<th>Reduction of EF</th>
<th>Normal EF</th>
<th>Slight</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF</td>
<td>4.8%</td>
<td>9.3%</td>
<td>18.8%</td>
<td>32.8%</td>
</tr>
<tr>
<td>Odds ratio multivariate</td>
<td>1.74</td>
<td>3.19</td>
<td>5.7</td>
<td>8.9</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>1.22–2.47</td>
<td>2.22–4.53</td>
<td>3.59–9.03</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: In the era of recanalisation at about 30% of unselected P after AMI are discharged with a slight, another 30% with a moderate or severe reduction of EF. Present data reveal no threshold. Increase in longterm mortality is associated with LVD in a stepwise manner. 3. With optimized medical treatment severity of LVD after AMI is a strong independent predictor of longterm mortality.
Cytokines Only Slightly Increased Under Optimized Medical Treatment in Unselected Patients With Advanced Heart Failure Due to Coronary Artery Disease

Thomas Kleemann, Caroline Bergmeier, Andreas Kilkowski, Matthias Sanger, Boris Fratant, Tanja Kolkmann, Dieter Nagel, Dietmar Selker, Josef Seinges. Herzinfarktklinik Ludwigshafen, Germany

Background: Recent studies suggest that cytokines apart from neurohor- mones increase with progression of chronic heart failure in patients (P) with left ventricular dysfunction (LVD). The aim of the study was to compare neurohormone and cytokine levels according to NYHA functional classes I to IV in unselected P with LVD due to coronary artery disease (CAD).

Methods: Serum levels of tumor necrosis factor alpha (TNF), interleukin-1 (IL-1), and ANP were measured in NYHA I/II and NYHA III/IV P with CAD and LVD. Correlation of cytokine levels with NYHA class and total body fat (assessed by DEXA scanning).

Results: IL-1 increased only slightly with severity of heart failure whereas IL-6 did not change significantly compared to those with NYHA I/II.

Conclusion: Despite normal NYHA class level, sympathetic nerve activity was increased in patients with mild HF. Myocardial iodine 123 scintigraphy is an useful noninvasive method to detect early alterations of sympathetic nerve activity.

Insulin Resistance in Chronic Heart Failure – TNF-Alpha, Norepinephrine, or Leptin-Related?

Wolfram Deehrner, Matthias Ruehmkors, Ian F. Goodsland, Constantin D. Davos, Andrew J. Coats, Steven D. Anker. Cardiac Medicine, National Heart and Lung Institute, London, UK

Background: Chronic heart failure (CHF) is an insulin resistant state, regardless of etiology. The cause of impaired insulin sensitivity remains unclear. Elevated levels of tumor necrosis factor (TNF)-α and norepinephrine (NE) have been implicated to cause impaired insulin sensitivity (SI) in CHF. The controversy of how leptin (L) affects SI is ongoing. We aimed to study the relative importance of these parameters in a large group of CHF patients.

Methods: In 62 CHF patients (age 62 ± 11 years; NYHA-class 2.6 ± 0.8, peak VO2 17.7 ± 6.3 ml/kg/min, LVEF 29 ± 15%, mean ± SD) we used an intravenous glucose tolerance testing (IVGTT) and the minimal model approach to assess SI and measured TNF-α, soluble TNF receptors (sTNFR) 1 and 2, NE, and L. Analyses were compared to a control group of similar age (n = 17).

Results: L was elevated in CHF patients compared to controls (7.7 ± 5.2 ng/ml vs 4.0 ± 0.7 ng/ml, p < 0.05) and NE (0.7 ± 0.6 mmol/l vs 0.7 ± 0.7 mmol/l, p = 0.01). No elevated levels were found for TNF-α but sTNFR 1 and sTNFR 2 were significantly increased in CHF patients (1296 ± 504 pg/ml vs 834 ± 289 pg/ml and 2495 ± 1109 pg/ml vs 1879 ± 921 pg/ml, respectively).

In CHF patients SI was 2.96 ml/kg/min /U/ml compared to 1.10 ml/kg/min, which was 34% lower in controls (p < 0.05).

In CHF there was no correlation of the SI with TNF-α nor with sTNFR 1 and sTNFR 2. No L did not correlate with SI (r = 0.2, p > 0.1). In contrast, we found a strong inverse correlation between SI and L (r = -0.48, p < 0.001). In stepwise regression L emerged as the only significant predictor of SI (β = 0.43, p < 0.001).

Conclusion: In CHF, insulin resistance is strongly and independently correlated with Leptin. However, in contrast to common thinking TNF-α and NE do not predict impaired insulin sensitivity.

Beneficial Effects of Comprehensive Cardiac Rehabilitation and Exercise Programs in Patients With Coronary Artery Disease After Coronary Stenting

Tadashi Hatake, Naohiko Menzaki, Harunori Konno, Kunihiro Kondo, Akiyoshi Kawashima, Shigeo Matsui, Yung-Sheng Hsu, Hideo Tamai, Hiromi Uehata. Shiga Medical Center for Adult Diseases, Moriyama, Japan

Background: Comprehensive cardiac rehabilitation (CCR) is known to result in improvements in multiple risk factors and increases in peak aerobic capacity (pV02 (ml/min/kg)) and prevents the decline in physical activity due to depressive state or the overactivity due to poor insight into disease in patients with coronary artery disease (CAD) after coronary stenting. Adjustment of daily physical activity due to CCR and augmentation of pV02 as a result of CCR may prevent restenosis after coronary stenting.

Methods: Ninety eight male patients (mean age 61 ± 11) with CAD underwent a successful coronary stenting were randomly allocated in the training group (T) or the control group (C) at 2 weeks after angioplasty. Seven month supervised AT level exercise training and mental supportive therapy were performed with the patients of T while ambulatory once a month was given to the patients of C. They performed cardiopulmonary exercise tests at 2 weeks, 4 months (M) and 7 M after coronary stenting. PeakVO2 and peakV02 were measured. Restenosis was defined as a residual stenosis at the time of follow-up angiography of more than 50% of luminal diameter. Analysis of % stenosis was done by blinded core lab OCA method.

Results: PeakVO2 and PeakV02 significantly increased in T while that in C did not change. The reference vessel size and the percent stenosis just after coronary stenting were comparable between the two groups. The restenosis rate in T was significantly lower than in C (at 4 M: T = 19.2%, C: 30.1%, at 7 M: T 20.3%, C: 36.0%).

Conclusion: CCR and exercise training programs prevent restenosis after coronary stenting in addition to contributing to reduction in total and cardiovascular mortality.

Short-Term Endurance Exercise Training Enhances Endothelium-Dependent Vasodilation in Healthy Premenopausal Women

Morton R. Binder, Jeffrey Greiwe, Ali A. Ehsani. Dept. of Medicine, Washington University School of Medicine, St Louis, Missouri, USA

Background: To test the hypothesis that short term endurance exercise training (RET) improve endothelium-dependent vasodilation (EDD), we examined the effect of training on flow mediated dilation (FMD) in response to L-arginine (a precursor of nitric oxide synthesis), since FMD is normal at baseline in healthy premenopausal women.

Methods: Eight women (age 26 ± 1.3 years old, mean ± S.E.) were studide during the late luteal phase of their menstrual cycle. Training consisted of running or cycling for 40 minutes per day, 6 days per week in a supervised training group (T) or the control group (C) at 2 weeks after angioplasty. Seven month supervised exercise training and mental supportive therapy were performed with the patients of T while ambulatory once a month was given to the patients of C. They performed cardiopulmonary exercise tests at 2 weeks, 4 months (M) and 7 M after coronary stenting. PeakVO2 and peakV02 were measured. Restenosis was defined as a residual stenosis at the time of follow-up angiography of more than 50% of luminal diameter. Analysis of % stenosis was done by blinded core lab OCA method.

Results: PeakVO2 and PeakV02 significantly increased in T while that in C did not change. The reference vessel size and the percent stenosis just after coronary stenting were comparable between the two groups. The restenosis rate in T was significantly lower than in C (at 4 M: T = 19.2%, C: 30.1%, at 7 M: T 20.3%, C: 36.0%).

Conclusion: CCR and exercise training programs prevent restenosis after coronary stenting in addition to contributing to reduction in total and cardiovascular mortality.
to 60 minutes per day in the fourth week in order to achieve 75% of their maximal heart rate during maximal exercise testing. FMD was determined by measuring the brachial arterial diameter with high resolution ultrasound before and after a 5 minute blood pressure cuff occlusion. FMD was also measured during the infusion of 1, 3, and 7 grams of L-arginine intravenously in the contralateral arm in an attempt to stimulate nitric oxide synthesis. Endothelium-independent vasodilation (EDD) was determined by measuring brachial arterial diameter before and after the sublingual administration of 0.4 mg of nitroglycerin.

**Results:** Maximal oxygen consumption was higher after training (35.2 ± 9.7 vs. 33.8 ± 8.8 mlO2/min, p = 0.001). EDD was worse before and after endurance training (121.5 vs. 122.8% of baseline diameter p = 0.58). FMD was marginally greater after 4 weeks of exercise training.

Maximal FMD per dose of L-arginine (% of baseline ± S.E.)

<table>
<thead>
<tr>
<th>Dose (g)</th>
<th>Maximal FMD (%) ± S.E.</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.0 ± 0.0</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>107.6 ± 1.8</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>106.6 ± 2.5</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>106.4 ± 1.7</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>112.1 ± 1.7</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>112.6 ± 2.5</td>
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</tbody>
</table>

**Conclusion:** Our data suggests that EDD is enhanced by short term training in healthy, non-smoking women with normal baseline endothelial function. This enhancement is measurable even in conduit arteries supplying untrained muscle groups suggestive of a systemic arterial adaptation to exercise.

**1073-122 Long-Term Exercise Training Leads to Sustained Improvement of Coronary Endothelial Function and Flow Reserve in Patients With Coronary Artery Disease**

Anamaria Wolf, Reiner Hambrecht, Axel Linke, Nina Schoene, Stephan Giebel, Sandie Hets, Jürgen Hoffer, Gerhard Schuler. Heart Center – University Leipzig, Leipzig, Germany

**Background:** Short-term supervised intermittent exercise training (ET) tests the potential to improve coronary endothelial dysfunction in patients (pts) with stable coronary artery disease (CAD). Aim of this prospective randomized in vivo study was to assess whether the short-term effects can be sustained over 6 months by home-based moderate ET.

**Methods:** 19 pts with stable CAD were randomized to a training (T, bicycle ergometer training 6/day for 4 weeks in hospital, 2/day at home for 5 months) or to an inactive control group (C). Coronary endothelial function in response to 7.2 ng/ml acetylcholine and flow reserve (CFR) after 2.4 mg adenosine/min were inversely measured at 0, 1, and 6 months (mo). Quantitative coronary angiography and Doppler flow wire were used to determine CFR (ID) and average peak velocity (APV).

**Results:**

<table>
<thead>
<tr>
<th>T 6 mo</th>
<th>T 12 mo</th>
<th>C 6 mo</th>
<th>C 12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>% ID</td>
<td>-1.6 ± 3.2</td>
<td>4.8 ± 3.2</td>
<td>8.9 ± 2.8</td>
</tr>
<tr>
<td>% APV</td>
<td>78.1 ± 15.8</td>
<td>141.6 ± 27.8</td>
<td>65.7 ± 19.8</td>
</tr>
<tr>
<td>CFR</td>
<td>2.8 ± 0.3</td>
<td>2.6 ± 0.2</td>
<td>3.2 ± 0.3</td>
</tr>
</tbody>
</table>

**Conclusion:** In pts with CAD high-intensity supervised ET significantly improves coronary endothelial function and CFR. However, these positive effects were not completely sustained by a moderate intensity home-based ET.

**1073-123 Effect of Exercise on Haemostatic Markers in Patients With Atrial Fibrillation**

Foo Li Saw Hoo, Andrew D. Gibson, Gregory Y.H. Liu. Haemostasis, Thrombosis and Vascular Biology Unit, University Department of Medicine, City Hospital, Birmingham B18 7OH, UK

**Background:** Although chronic atrial fibrillation (AF) is known to confer a hypercoagulable state, it is uncertain whether this is further altered by exercise. Methods: We measured factors v and VIII, thrombin-antithrombin complex (TAT), plasminogen activator inhibitor-1 (PAI) ng/ml, fibronolysis, soluble P-selectin (sP-sel, ng/ml), platelet activation (all by ELISA) and fibrinogen (fb, g/l, Clauss method) in 20 AP patients not on any antithrombotic therapy (15 men; mean age 65 ± 11 years). All had treadmill exercise test (ET) (standard Bruce protocol) achieving a mean workload of 4.9 ± 1.7 metabolic equivalents and a mean exercise time of 4.0 ± 0.5 minutes. Bloods were taken at baseline, immediately and 20 minutes post-ET. Baseline levels were compared to matched healthy controls in sinus rhythm. (sfi, Fib, mean ± SD, PAI, sP-sel median and interquartile range)

**Results:**

<table>
<thead>
<tr>
<th>Exercise test</th>
<th>Acid Et</th>
<th>CR-m</th>
<th>After 6 min P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration (min)</td>
<td>4.1 ± 4</td>
<td>10.5 ± 3.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate at rest (bpm)</td>
<td>109 ± 21</td>
<td>137 ± 20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate at peak (bpm)</td>
<td>137 ± 21</td>
<td>139 ± 24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Delta Systolic BP (mmHg)</td>
<td>23 ± 10</td>
<td>19 ± 10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oxygen Saturation at risk (%)</td>
<td>82 ± 10</td>
<td>82 ± 10</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Conclusion:** Exercise tests using modified Bruce protocol were performed in 20 consecutive GUCH patients who presented with symptomatic atrial flutter (AF) during and again 24–48 hours after DC conversion to sinus rhythm (SR). Diagnoses were one ventricle 9 (5 with Fontan type surgery), transposition of great arteries 4 (3 had Mustard and 1 arterial switch), hypertrophic cardiomyopathy (HCM) 3, closed atrial septal defect 2 and other lesions 2. Age at study was 21-95 years, 11 females. The first AF attack was in 4 and recurrent in 17 patients.

**1073-125 Effects of Atrial Flutter vs Sinus Rhythm on Exercise Tolerance in Grow-Up Congenital Heart (GUCH) Patients**

Wei Li, Jane Somerville. Royal Brompton Hospital and Imperial College School of Medicine, London University, UK

**Background:** Atrial flutter (AF) is common in GUCH patients and leads to deterioration of patients' effort tolerance and functional ability Indices.

**Methods:** Exercise tests using modified Bruce protocol were performed in 20 consecutive GUCH patients who presented with symptomatic atrial flutter (AF) during and again 24–48 hours after DC conversion to sinus rhythm (SR). Diagnoses were one ventricle 9 (5 with Fontan type surgery), transposition of great arteries 4 (3 had Mustard and 1 arterial switch), hypertrophic cardiomyopathy (HCM) 3, closed atrial septal defect 2 and other lesions 2. Age at study was 21-95 years, 11 females. The first AF attack was in 4 and recurrent in 17 patients.

**Results:**

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</tr>
<tr>
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**Conclusion:** Exercise tests using modified Bruce protocol were performed in 20 consecutive GUCH patients who presented with symptomatic atrial flutter (AF) during and again 24–48 hours after DC conversion to sinus rhythm (SR). Diagnoses were one ventricle 9 (5 with Fontan type surgery), transposition of great arteries 4 (3 had Mustard and 1 arterial switch), hypertrophic cardiomyopathy (HCM) 3, closed atrial septal defect 2 and other lesions 2. Age at study was 21-95 years, 11 females. The first AF attack was in 4 and recurrent in 17 patients.

**Results:**

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</tbody>
</table>
12 minutes in 4 patients who were not taking antiarrhythmic medicine. With sinus rhythm exercise was terminated mainly because of fatigue or breathlessness. Inability to maintain sinus rhythm in GUCH patients. Antimo Papa, Giuseppe Furgi, Nunzio Guerra, Claudio Calabrese, Fondazione "Salvatore Maugeri", Telese Terme, BN, Italy

Background: In patients with coronary artery disease, brief periods of exercise following by resting lead to reduce the severity of exercise-induced ischemia (warm-up phenomenon). This phenomenon, which may represent a clinical counterpart of ischemic preconditioning has not been investigated in elderly patients.

Methods: Two consecutive ergometric exercise stress tests (Tests 1 and 2) were performed in 18 adult (mean age: 55 ± 8 years) and 15 elderly (mean age: 73 ± 5 years) patients with chronic stable angina and comparable coronary anatomic findings. Time to 1 mm ST segment depression (STSD) in seconds, maximum ST segment depression (maxSTSD) in mm, and recovery time of ST depression to <1 mm of baseline (Rect) in sec were considered.

Results: The results are shown in the following table.

<table>
<thead>
<tr>
<th></th>
<th>Adult</th>
<th>Elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test 1</td>
<td>STD</td>
<td>434 ± 154</td>
</tr>
<tr>
<td>Test 2</td>
<td>304 ± 40</td>
<td>300 ± 82</td>
</tr>
<tr>
<td>p &lt; 0.001 vs Test 1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: A previous exercise following by resting is able to reduce the ischemia induced by a successive exercise stress test in adult but not in elderly patients with coronary artery disease. Moreover, our results confirm experimental data on the age-related reduction of ischemic preconditioning.

827 Exercise Tolerance in Heart Failure

Monday, March 13, 2000, 9:15 a.m.-10:30 a.m.
Anahem Convention Center, Room 304A

827-1 Relationship Between Reduced Pulmonary Diffusing Capacity and Excessive Ventilatory Response to Exercise in Patients With Chronic Heart Failure

Richard Gervasoni, Jérôme Brunet, Laurent Poirier, Christian Prillaut, Jean-Marc Davy, Robert Genfaux, Patrick Messner-Pellenc. Departments of Cardiology, Department of Physiology, University-Hospital of Montpellier-Nimes, France

Background: Chronic heart failure (CHF) is characterized by exercise intolerance. Excessive ventilatory response contributes to exercise limitation. The determinants of exercise hyperventilation remain unclear. In CHF, pulmonary diffusing capacity for carbon monoxide (DLCO) is reduced at rest and mostly impaired during exercise. The aim of this study was to determine the relationship between impaired diffusing capacity during exercise and excessive ventilatory response.

Methods: Maximal peak oxygen consumption (pVO2) was assessed during exercise by pulmonary exercise test in 14 control subjects, in 15 CHF patients (pts) with pVO2 < 16 ml/kg/min (Group 1) and in 8 CHF pts with pVO2 > 16 ml/kg/min (Group 2). DLCO (mmHg/ml/min/SD) and DLCO/alveolar volume (VA) were simultaneously measured at rest and during exercise, both by intrabronch method. Blood gases were measured at rest and at maximal exercise (max E). Ventilatory response was calculated during exercise (VE/VO2 slope). p < 0.01 and maximal DLCO (22.3 ± 12.4 = 47.6 ± 18.5, p = 0.001) were lower in all CHF pts vs control. Rest-DLCO, max-DLCO, max-DLCO/VA were built inversely correlated with the VE/VO2 slope. Regarding to the severity of CHF, DLCO/VA was reduced at rest and did not increase during exercise only in group 2, suggesting an impairment in alveolar-capillary capacities. Nevertheless, no arterial desaturation at max E with an increase difference between alveolar and arterial PO2, despite altered diffusing capacity were observed.

Conclusion: This study supports a relationship between reduced diffusing capacity during exercise and excessive ventilatory response through an adaptive response: excessive hyperventilation exercise, inducing higher difference between alveolar and arterial PO2, preserves stable normal blood gases, despite altered diffusing capacity at exercise observed in more severe CHF pts.

827-2 Decreased Submaximal Exercise Tolerance and Increased Sympathetic Activation In Response to Cold Exposure in Patients With Congestive Heart Failure

Michel White, Martin Junassou, Jean-L. Rouleau, Johanna Marquis, Nicole Poltrax, Anique Ducharme, Jean-Claude Tardif, Lizanne Bussieres. Montreal Heart Institute, Montreal, Quebec, Canada

Background: Cold exposure decreases ischemic threshold and exercise duration in patients with coronary artery disease. The purpose of this study was to investigate the effects of cold exposure on exercise tolerance assessed by submaximal endurance protocols, and on systemic adrenergic activation in patients with congregate heart failure (CHF) caused by coronary artery disease or dilated cardiomyopathy.

Methods: Twelve patients with CHF NYHA class II-III, aged 61 ± 9 years (mean ± SD), mean EF = 24 ± 5% (18-34%) all treated with an ACE-inhibitor but not treated with a β-blocker, and 10 age-matched healthy volunteers (HV) performed a VO2 max on a Ramp protocol and two endurance exercise tests < 4.3% above the aerobic threshold at 20°C and 4°C. Heart rate and blood pressure were measured at baseline and at the time of exhaustion.

Results: Patients with CHF had lower VO2 max [19 ± 4.5 (CHF) vs 32.9 ± 4.2 ml/kg/min (HV), P < 0.03]. Exercise duration was similar at 20°C and at 4°C in HV (1366 ± 486 (20°C) vs 1500 ± 622 sec (4°C), P = 0.29). In contrast, exercise-time decreased by 20 ± 22% at -8°C in patients with CHF (1000 ± 394 (20°C) vs 821 ± 431 sec (-8°C), P = 0.005). VO2 increased to the same extent in HV and CHF patients at 20°C (1668 ± 1038 (CHF) vs 1705 ± 828 mg/l (HV)) but tend to increase more in CHF patients at -8°C (2501 ± 2048 (CHF) vs 1543 ± 1081 mg/l (HV), P = 0.07). Exercise was limited by dyspnea in all patients.

Conclusion: As opposed to healthy volunteers, patients with symptomatic CHF with or without CAD exhibited decreased exercise capacity and likely increased systemic adrenergic activation in the cold as measured by submaximal endurance protocols. This provides an additional rationale for using β-adrenergic blockade in patients with CHF frequently exposed to cold.

827-3 Prognostic Value of the "Circulatory" Power During Exercise in Patients With Heart Failure

Jean-Yves Tabet, Damien Logeart, Pierre Bourgoin, Chabnam Gulfi, Christine Alonso, Alain Cohen Solal. Hopital Beaujon, Clichy, France

Background: Cardiac power (cardiac output x arterial pressure) is measured by catheterization during exercise was shown to have a greater prognostic value than the classical exercise variables in patients with chronic heart failure (CHF). We wondered whether this measurement non invasively approached had similar value.

Methods: 175 CHF patients (ejection fraction < 40%) underwent cardopulmonary exercise testing; the product of VO2 by arterial pressure equals cardiac power > arteriovenous O2 difference ("circulatory" power) was calculated at peak exercise; its prognostic value was assessed after a mean follow-up of 26 months.

Results: Age was 53 ± 10 years and ejection fraction 25 ± 10%. The mean value of the maximal circulatory power was 243 ± 107 mm Hg.1.01 and 3199 ± 1299 mm Hg.1 kg.1. Patients who died or underwent transplantation has lower circulatory power than those surviving (2477 ± 905 vs 3575 ± 1273 mm Hg.1 kg.1, p = 0.0001). By univariate analysis, both variables had high
prognostic value ($x^2 = 18$ and 26 respectively, both $p < 0.0001$). Peak VO2 had
the highest $x^2$ value ($x^2 = 52$). However, by multivariate analysis, the
circulatory power indexed by weight or predicted values ($x^2 = 4.4$ and 5.1, $p < 0.05$)
was the only predictor of outcome whereas peak VO2 was not any more.

**Conclusion:** The "circulatory" power, product of systolic arterial pressure
by VO2, that integrates cardiac, vascular and peripheral factors, appears as a
surrogate of cardiac power that does not necessitate invasive measurements.
Its peak exercise value appears as a very powerful prognostic factor.

**827-4**

Comparison of the Prognostic Value of Left Ventricular Filling and Peak Oxygen Uptake in Patients With Heart Failure

Jean-Yves Tabet, Damien Logeat, Chabnam Guiti, Pierre Emmasat, Christina Alonso, Alain Cohen Solal, Hopital Beaujon, Clichy, France

**Background:** Whether a left ventricular (LV) restrictive doppler mitral inflow
pattern has better prognostic value than peak oxygen uptake (VO2) in chronic
heart failure (CHF) is unknown.

**Methods:** 100 consecutive CHF patients (ejection fraction < 45%) under-
went exercise testing after Doppler evaluation; prognosis (death, transplantation-
planning) was assessed after a mean follow-up of 17 months.

**Results:** Forty-five patients (age 55 ± 10 years) were in NYHA class II,
47 in class III and 8 in class IV. Ejection fraction was greater Group 1 (non
restrictive pattern: E/A mitral wave ratio < 1 or > 1 and < 2 with E deceleration
time (DT) > 140 msec) than in Group 2 patients (restrictive pattern: E/A > 2
or > 1 and > 2 with E deceleration time < 140 msec) (29 ± 9 vs 22 ± 10, p
< 0.05). Peak VO2 was lower in Group 2 (17 ± 4 vs 22 ± 5 ml/min/m2; p
= 0.05) was the only predictor of outcome whereas peak VO2 was not any more.

**Conclusion:** Although the LV pattern is a strong predictor of outcome in
CHF patients, independently of the ejection fraction, peak VO2 remains a
more powerful prognostic variable.

**827-5**

Percutaneous Septal Ablation in Patients With Hypertrophic Obstructive Cardiomyopathy Results in Improvement of Exercise Capacity

Peer Ziemssen, Lothar Faber, Jürgen Schlichting, Werner Meyners, Dieter Horstkotte, Hubert Seggewiss, Dept. of Cardiology, Heart Center NRW, Ruhr-University Bochum, Bad Oeynhausen, Germany

**Background:** Pts. with HOCM show an improvement of symptoms after per-
cutaneous septal ablation (PTSA). We analyzed exercise capacity by cardio-
 pulmonary vascular testing (CPX) in symptomatic patients with HOCM before
and after PTSA.

**Patients and Methods:** 15 consecutive pts. (46 ± 13 years, 9 men, NYHA
2.8 ± 0.1) underwent L-VVX using a bipo邪 ergometer ramp protocol (1 W
watts/min). The following variables were measured before and 3 as well as 12 months after PTSA: peak oxygen consumption (%VO2), pVO2 at anaerobic threshold (AT), oxygen pulse (O2 puls), maximal work load (WL), and determined by echocardiography left
ventricular outflow tract obstruction at rest (LVOTGR) as well as at Valsalva
(LVOTGV).

**Results:** The table shows the CPX data and LVOTG of all pts.

**Conclusions:** After PTSA symptomatic pts. with HOCM show an
improvement of subjective as well as objective measurements of exercise ca-
pacity. These changes are predominantly seen during the longer-term fol-
low-up due to the previously documented remodeling after circumscribed
thoracoscopic interaction.

**828**

**ORAL**

**828-1**

Influence of the Passive ACORN® Cardiac Support Device on Systolic and Diastolic Left Ventricular Function

Franz X. Kleber, Steffen Sonntag, Heike Krebs, Katrin Stantke, Birgit Rombach, Wolfgang Konertz, Dept. of Cardiology UKD, Dept. of Cardiovascular Surgery Charité, Humboldt University Berlin, Germany

**Background:** Heart failure is characterized by progressive increase in ventric-
ular volume, dilation and reshaping of ventricles and deterioration of homo-
dynamics. According to La Place's law ventricular chamber size importantly
contribuates to afterload, thus limiting the heart's ability to translate toerean
development into volume work. The surgical placement of a passive con-
straining device over the ventricles could halt ventricular dilatation or decrease
ventricular volumes. However it might unfavourably influence diastolic func-
tion by directly limiting filling or by an excessive fibrotic response leading to
constrictive pericarditis.

**Methods:** In 7 male patients (age 46 ± 11 yrs; baseline LVEF 23%; median
NYHA III) we studied left ventricular function 3 months after implantation of an
ACORN® cardiac support device, 5 of whom had preimplantation studies for
comparison (see below). Simultaneous right and left ventricular pressures
were analyzed, pressure volume curves were constructed by microanomet-
erie tip LV pressure recordings and biplane contrast ventriculography applying
Simons rule. The time constant of isovolumic relaxation (c), the chamber
stiffness constant and the slope of the end-systolic PV relationship (ESPV slope)
were calculated.

**Results:** No patient showed clinical signs of constriction, though 1 pa-
tient was still congested when investigated. LV-RV pressure differences were
preserved and relaxation as well as late diastolic function were unimpaired
anteriorly using CPX. However, pressure volume curves were constructed by microanome-
ter tip LV pressure recordings and biplane contrast ventriculography applying
Simons rule. The time constant of isovolumic relaxation (c), the chamber
stiffness constant and the slope of the end-systolic PV relationship (ESPV slope)
were calculated.

**Conclusions:** The ACORN® cardiac support device does not have any
unfavourable constricting effects on the heart 3 months after implantation. Systo-
lic and early diastolic left ventricular function is improved, late diastolic stiff-
ness is not increased. Further safety and efficacy studies are needed to con-
firm these initial results.

**828-2**

Short-Term Safety of the Acorn Cardiac Support Device in Patients With Advanced Heart Failure

Wolfgang Konertz, Birgit Rombach, Holger Hotz, Michael Zywoski, Steffen Sonntag, Franz X. Kleber, Harri N. Sudfelder, Dept. of Cardiology Charité, Humboldt University Berlin, Germany; 1:Heart and Vascular Institute, Detroit, Michigan, USA

**Background:** The Acorn Cardiac Support Device (CSD), a preformed-knitted
polyester device surgically placed over the cardiac ventricles, has been shown
to prevent progresive LV remodeling and improve LV ejection fraction in dogs
with heart failure (HF). As an initial safety study, the CSD was implanted in 16
patients (14 males, 2 females; age = 56 ± 3 yrs) with advanced HF (NYHA
class II ± III).

**Results:** The table shows the CPX data and LVOTG of all pts.

**Conclusions:** After PTSA symptomatic pts. with HOCM show an
improvement of subjective as well as objective measurements of exercise ca-
pacity. These changes are predominantly seen during the longer-term fol-
low-up due to the previously documented remodeling after circumscribed
thoracoscopic interaction.
confirm safety before efficacy trials are undertaken in patients with HF.

Methods: Of the 16 patients, 11 had concomitant mitral valve repair or replacement, 1 had concomitant LVAD placement and 1 received only the CSD. The CSD was placed while on bypass but with the heart beating, was anchored at the AV groove and tailored anteriorly to fit around the ventricles.

Results: All patients tolerated the surgery with no complications. Two patients died from non-CSD related causes 25 and 40 days post-operatively; 1 from heparin-induced thrombocytopenia and 1 from complications of a sudden death having had history of VT. None of the remaining 14 patients had any CSD related adverse events during an average 2.9 ± 0.3 months follow-up. Ten of 14 patients have completed a 1 month follow-up and none had atrial ligation or re-Discl/Disrup findings. Changes were also noted in their resting physiology. Their pre- and 1 month post-implant findings are in the table.

Conclusion: The results to date indicate that the Acorn CSD is safe and well tolerated by patients with advanced HF. Longer follow-ups are needed to confirm safety before efficacy trials are undertaken in patients with HF.

Methods: Device Based Left Ventricular Shape Change Immediately Reduces Left Ventricular Volume and Increases Ejection Fraction in a Pacing Induced Cardiomyopathy Model in Dogs: A Pilot Study

Patrick M. McCarthy, Kyotoku Fukumachi, Masami Takagaki, Guy Armstrong, James B. Young, Cyril J. Schweich, Jr., Todd J. Mortier, Marc R. Raffe.

Cleveland Clinic Foundation, Cleveland, OH; Myocor Inc., Plymouth, MN, USA

Background: Left ventricular (LV) remodeling in heart failure leads to dilatation, ventricular shape alteration, and physiologic changes that result in depressed LV contractile function. We tested the hypothesis that a LV shape change from globular to bi-lobar reduces ventricular wall radius of curvature, reduces wall stress and improves contractile function in an experimental heart failure model.

Methods: Heart failure was induced in six healthy mongrel dogs implanted with transvenous pacemakers by pacing at 230 bpm for an average of 23 days. Induction progress was monitored weekly and considered complete when transthoracic 2D echocardiography (2DE) ejection fraction (EF) was reduced to 50% of prepacing value. A novel device, the Myocor Myosplint", was surgically implanted in the LV to produce an estimated 20% or 30% reduction in wall stress by changing LV shape. Shape change was achieved by placing 3 Myosplint" devices perpendicular to the LV long axis and drawing the opposing LV walls inward, creating a symmetric, bi-lobar LV. Cardiac output (CO), stroke volume (SV), heart rate (HR), and systemic blood pressure (SBP) were measured prior to, and immediately following, 20% and 30% stress reduction levels. Cardiac output measurements for end diastolic volume (EDV) and end systolic volume (ESV) and EF were collected. Comparisons were made using paired t tests corrected for multiple comparisons.

Results: Mean decreases in EDV (-16.5 ml, -27.6 ml) and ESV (-22.2 ml, -29.7 ml) were significant (p < 0.05) at 20% and 30% stress reduction levels yielding increases in mean EF from 0.27 to 0.30 at 20% and from 0.28 to 0.38 at 30% stress reduction levels, respectively. HR, SV, CO, and SBP were unchanged from baseline.

Conclusions: Shape change produced by the Myocor Myosplint" immediately improved EF and reduced ventricular volumes. Hemodynamic function remained stable following LV shape change.

Methods: We studied 57 patients (age = 59 ± 8 years, 46 men) with EF < 40% reformed for CABG with dobutamine (up to 40 µg/kg/min) etroco reinjection 201 thallium SPECT and radionuclide ventriculography (RNV) at rest and at low dose dobutamine (5-10 µg/kg/min) before and 3 months after CABG.

Results: An increase of resting EF > 5% occurred in 12 patients (group A) after CABG (EF = 34% before and 46% after CABG), whereas the remaining 45 patients (group B) failed to demonstrate such increase (EF = 34% before and 38% after CABG). A significant increase of EF from rest to low dose dobutamine RNV occurred before and after CABG. However, the magnitude of increase was more significant after than before CABG in group A (12% vs 7%) as well as in group B (13% vs 7%, both p < 0.001). Patients of both groups demonstrated a significant reduction of stress, rest and ischemic perfusion defect scores after CABG. However, the percentage of reduction of rest perfusion defect score was more significant in group A than in group B (80% vs 38%, respectively, p < 0.001).

Conclusion: In patients with reduced EF, CABG induces a significant improvement of resting myocardial perfusion and EF response to inotropic stimulation even in absence of improvement of resting EF.

Does Improvement in Left Ventricular Ejection Fraction Predict Long Term Survival After Coronary Artery Bypass Surgery in Patients With Ischemic Cardiomyopathy?

Mohammad Isteihir, Michael S. Lauar, Nicholas G. Smedira, Eugene Blackstone, Imran Afidi. Cleveland Clinic Foundation, Cleveland, OH, USA

Background: Left ventricular ejection fraction (LVEF) is a major determinant of survival in patients with coronary artery disease. Coronary artery bypass surgery (CABG) has been shown to improve LVEF in selected patients with ischemic cardiomyopathy.

Objective: The purpose of this study was to determine whether improvement in LVEF after CABG predicts long term survival of patients with ischemic cardiomyopathy.

Methods: We reviewed CABG database at our institution from 1990-97 to identify patients with LVEF ≤ 35%, who survived isolated first CABG and underwent echoangiography within 3 months prior to and after CABG. An improvement in LVEF of ≥ 5% was considered significant.

Results: Study criteria were met by 131 pts (50 male, age 64 ± 11 years). After CABG there was significant improvement in LVEF (31 ± 10% vs. 27 ± 7%, P < 0.0001). In 63 patients (48%) LVEF improved ≥ 5%. During a mean follow up of 3.5 years 48 patients died (37%). Although, a trend toward improved early survival was noted in the group with post-operative improvement in LVEF, there was no difference in late survival (figure).

Conclusion: Contrary to popular belief, improvement in LVEF after CABG did not predict long term survival of patients with ischemic cardiomyopathy.

11:45 a.m.

POSTER

New Methods to Assess Myocardial Function

Monday, March 13, 2000, Noon—2:00 p.m.
Anahiem Convention Center, Hall A
Presentation Hour: 1:00 p.m.—2:00 p.m.

Correlation Between Endocardial Voltage Mapping and Myocardial Perfusion: Implications in the Assessment of Myocardial Ischemia

Smiuel Fuchs, Matie Shou, Anthony Pierre, Martin B. Leon, Ron Komowski. The Cardiovascular Research Foundation, Washington Hospital Center, Washington, DC, USA

Background: Recent experimental and clinical experiences using a non-invasive 3 dimensional (3D) left ventricular (LV) mapping system showed considerable alterations in voltage amplitudes detected in endocardial versus
sustaining myocardial ischemia and/or infarction. However, the relationship between measured potential voltions and myocardial perfusion has not been defined.

Methods: In a pig model of chronic myocardial ischemia (n = 20), LV endocardial unipolar voltage (UpV) mapping was performed using the Biosense' tool to relate specific gene products to phenotype in transgenic mice. Echocardiography was used to assess regional myocardial thicknessening (MT), and fluorescent microspheres (4 × 10^8 injection) were used to quantify rest regional myocardial blood flow (MBF) in ischemic (LCX) and non-ischemic (LAD) regions.

Results:

A positive correlation was found between UpV and rest endocardial (but not epicardial) blood flow using the regression formula: UpV (mV) = 7.8 + 5.9 × MBF

Conclusions: Chronic myocardial ischemia, resulting in reduced perfusion and function at rest (i.e. hibernating myocardium), is characterized by a significant reduction (~25%) in endocardial voltage potentials which correlates well with reduced endocardial blood flow at rest. Thus, LV guided endocardial voltage mapping can identify and localize the severity of regional endomyocardial hypoperfusion at rest.

1094-121 Different Effect of Enalapril on Hypertrophy and Metabolic Abnormalities in Two Models of Pressure Overload Induced Left Ventricular Hypertrophy

Simon N. Allo, Susan M. Polizzi, Charles J. Storey, Theodore Abraham, Craig R. Malloy, UT Southwestern Medical Center Dallas, Texas, USA

Background: Left ventricular hypertrophy (LVH) is associated with increased cardiovascular morbidity and mortality, which are reduced by normalization of LV mass with therapy. Hearts with LVH, even when mild, have increased glucose oxidation and decreased long chain fatty acid oxidation. It is not known if the profile of energy sources also returns to normal after therapy with angiotensin converting enzyme inhibitors. We examined the effects of enalapril on the cardiovascular morbidity and mortality, which are reduced by normalization of LV mass with therapy. Hypertrophic potential LVH in both models. Despite complete regression of LVH in SH rats by HE, fatty acid oxidation remained decreased. In AB animals, control of BP and metabolic abnormalities correlate with LV hypertrophy.

Methods: Two animal models of pressure overload induced LVH (aortic banded (AB) and spontaneously hypertensive (SH) rats) were compared to normal subjects; Group I-40 with dominant early diastolic LV filling, age 43 ± 10 years and Group II-20 with dominant late diastolic filling, age 60 ± 10 years. Systolic and diastolic myocardial velocities were determined in 8 groups, between the LV base and apex. Early and late diastolic velocities are shown in the table (all values in m/s).

<table>
<thead>
<tr>
<th>Group</th>
<th>Early Diastolic Velocities (m/s)</th>
<th>Late Diastolic Velocities (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base</td>
<td>0.15 ± 0.03</td>
<td>0.12 ± 0.02</td>
</tr>
<tr>
<td>Mid-cavity</td>
<td>0.13 ± 0.03</td>
<td>0.09 ± 0.02</td>
</tr>
<tr>
<td>Apical</td>
<td>0.06 ± 0.02</td>
<td>0.05 ± 0.02</td>
</tr>
</tbody>
</table>

*P<0.001 E & A velocities in the 2 groups.

Conclusions: Although systolic velocity propagation did not differ in the two groups early diastolic ones were much lower and late diastolic higher in late filling ventricles. The higher apical velocity of atrial contraction in the same group suggests an accentuated mechanical atrial activity balancing the fall in early diastolic velocities with age.

1094-123 Multiple Frequency Volume-Conductance Catheter Provides True Volume in the Mouse Left Ventricle

Marc D. Feldman, Yi Mao, Gregory L. Freeman, Jonathan W. Valvano, John A. Pearceo, University of Texas Health Science Center, San Antonio, Texas, USA

Background: Transgenic mice provide a valuable way to relate specific gene products to phenotype. Assessment of cardiac performance in the pressure-volume plane would be useful to help assess how specific genes impact on cardiac physiology. Volume-conductance technology can generate an instantaneous left ventricle (LV) volume signal, but is limited by current leakage into the myocardium. We hypothesized that assessing conductance across a range of frequencies could solve this problem.

Methods: Myocardial and blood resistivity, LV end-systolic volume (ESV), end-diastolic volume (EDV), and stroke volume (SV) were determined in 8 mice. We combined these data with an analytical approach to extract LV blood volume from the raw conductance signal, and compared it to the current standard conductance technique (hypertonic saline technique).

Results: The figure shows that mouse myocardial resistivity varies with frequency while blood resistivity does not. Thus, EDV and ESV vary with frequency while SV does not. The table shows the multiple frequency method gave similar results to the standard method.

<table>
<thead>
<tr>
<th>Study</th>
<th>EDV (μL)</th>
<th>ESV (μL)</th>
<th>SV (μL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple frequency</td>
<td>21 ± 2</td>
<td>16 ± 1</td>
<td>5 ± 2</td>
</tr>
<tr>
<td>Standard method</td>
<td>28 ± 4</td>
<td>13 ± 10</td>
<td>10 ± 4</td>
</tr>
</tbody>
</table>

Individual values increased similarly (EDV vs. 0.9, ESV vs. 0.7, SV vs. 0.8).

Conclusions: The multiple frequency-volume-conductance system can empirically solve for left ventricular blood volume in the mouse. It is a new tool to relate specific gene products to phenotype in transgenic mice.

1094-124 Effect of Increased Afterload on Left Ventricular Function in Mice

Marc D. Feldman, Yi Mao, Gregory L. Freeman, University of Texas Health Science Center, San Antonio, Texas, USA

Background: The availability of the transgenic mouse as a tool to relate cardiac phenotype to specific gene alterations has increased interest in routine physiology, of which little is known. Specifically, it is unknown how the mouse left ventricle (LV) responds to a sustained increase in afterload. Accordingly, we determined the effects of increased steady-state increases in afterload on the LV pressure-volume relationship.

Transmission of Atrial Systolic Velocity in the Left Ventricle: Umea General Population Survey Study

Michael Y. Henein, Andesh Waldenstrom, Kjell Karp, Per Lindqvist, Elnadii Kazzam, Derek G. Gibbon, Umea University Hospital, Sweden; Royal Brompton Hospital, London, UK

Background: The left atrium functions in systole as a reservoir and in late diastole it contributes to the atrioventricular active mechanical contraction.
Global Diastolic Function

Jonathan M. Milden, Mark S. Sessoms, Jennifer B. Lisauskas, Andrew W. Bowman, Jennifer B. Lisauskas, Sandor J. Kovacs, Cardiovascular Biophysics Laboratory, Washington University in St. Louis, MO, USA

Background: The best invasive index of diastolic function (DF) is the LV end-diastolic pressure, defined at a single point in diastole. Noninvasive DF indexes have relied on selected attributes of the Doppler E- and/or A-wave, or pulmonary venous flow patterns. Systolic ventriculo-arterial impedance (Z,) to be the ratio of diastolic LV pressure (Pd) to transmitral flow (Qd) during early-rapid filling (E-wave).

Methods: Simultaneous Doppler E-waves and micromanometric (Millar) Pd were recorded during diagnostic catheterization in 19 subjects (IO normal, 9 abnormal). Fourier analysis of model-based image processed E-waves images were subjected to analysis via model-based image processing to provide Ees. To compute ESPR, the linear ESPVR was determined via the single-beat estimation method of Sengazi et al. The figure schematically shows the ESPVR as well as the ESPRE (blue) to Z = measured (orange) and Z = estimated (green) relation.

Results: For n = 5, Ees = 38.4 ± 2.9% of the ESPR. Ees = 27.4 ± 10.5%, and Q = 34.2 ± 11.6%. Note that the sum of Ees and Ees.wave is <100% of ESPR.

Conclusion: Sufficient potential energy (elastic strain) is stored at end-systole to account for untwisting during isovolumic relaxation and to act as a source of LV recoil to power suction-related, b-wave generation. Contraction of mechanically coupling systole to diastole. It reinforces the heart’s role as a mechanical suction-pump. Application to pathologic states is in progress.

Electroanatomical Left Ventricular Mapping (NOGA®) for Prognostication of Functional Recovery

Karl-Christian Koch, Alexander Sasse, Monika Wunderlich, Elisabeth Ostwald, Christoph Steilbrink, Udalrich Buell, Peter Harath, Juergen vom Dahl, University Hospital, Aachen, Germany

Background: Electroanatomical mapping with a nonfluoroscopic, catheter-based system (NOGA®, Boston) may be a method to assess myocardial viability. In this study we predict the value of the regional electrogram amplitude measured by NOGA for wall motion recovery was assessed.

Methods: Twenty-nine patients (pts; 24 male 5 7 years with prior (2 weeks) myocardial infarction undergoing single- or multi- vessel PCTA were studied. Coronary angiography and laserangiography were performed prior to PCTA and at 6 month follow up. For regional wall motion analysis the centerline method was used and regional wall motion expressed as SD/chord. Prior to PCTA, endocardial electrograms were mapped using the NOGA® system. The left ventricle was divided into 12 regions and the regional mean amplitude of the unipolar electrogram was calculated. Based on previous univariate studies using FVC/PRT, a regional mean amplitude of 7 mV was used as threshold for viability assessment.

Results: Twenty-two patients had a good PCTA result at 6 month follow-up angiography. Regional wall motion improved from -2.4 ± 0.9 SD/chord (p < 0.01) in infarct regions with electrogram amplitudes >7 mV (n = 12), whereas regional wall motion worsened from -2.3 ± 0.5 SD/chord (p < 0.01) in infarct regions with amplitudes <7 mV (n = 10). Similarly, left ventricular ejection fraction improved from 50 ± 18% to 60 ± 11% (p = 0.03) in patients with preserved electrogram function whereas ejection fraction did not change (54 ± 8% to 51 ± 11%, p = 0.41) in
the remaining patients. The positive predictive value of NOGA for wall motion recovery > 0.628/standard deviation was 88% and the negative predictive value was 80%.

Conclusion: These data suggest that the mean regional amplitude of the electrogram, derived from NOGA mapping, may predict improvement in wall motion abnormality after successful revascularization.

**1095-143 Validation of Real-time 3D Echocardiography for Quantifying LV Volumes in the Presence of a LV Aneurysm: In Vitro and Clinical Studies**

Jian Xin Qin, Takahiro Shiota, Hirokazu Majumdar, Michael S. Frenckenberg, Lisa A. Ardell, Jill A. Odabashian, Richard D. White, James D. Thomas. The Cleveland Clinic Foundation. Cleveland, OH, USA

Although LV volume can be obtained satisfactorily in many patients by 2DE, it is limited when applied for patients with LV aneurysm. The purpose of this study was to validate the accuracy of real-time 3D echocardiography (3DE) for quantitating aneurysmal LV volumes.

Methods: 3DE and 2DE systems were used to acquire images of 7 aneurysmal balloons and of 34 patients (14 with chronic LV aneurysms and 20 with normal LV). LV volume was measured with a rotated apical 6-plane method by 3DE and with Simpson’s rule by 2DE. Magnetic resonance imaging (MRI) was used for validation in the patient study.

Result: In the in vitro study, the volume range of aneurysmal balloons was 150 to 395 ml. The volumes calculated by 3DE and 2DE correlated well with actual values. However, 3DE was more accurate than 2DE (mean difference: -7 to 7 ml vs 27 to 12 ml, p = 0.0002). In the clinical study, LV aneurysmal and non-aneurysmal volumes were 143 ± 47 ml and 91 ± 74 ml in control group and 290 ± 89 ml and 159 ± 83 ml in aneurysm group. Excellent correlations and agreements between 3DE and MRI for LV volumes were found. Although 2DE correlated well with MRI in patients without aneurysma, the r-value decreased and A increased in patients with aneurysm (Table).

**Table:**

<table>
<thead>
<tr>
<th>3DE vs 2DE</th>
<th>3DE vs MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Aneurysm</td>
</tr>
<tr>
<td>r-value</td>
<td>0.86</td>
</tr>
<tr>
<td>Δ (ml)</td>
<td>-13 ± 18</td>
</tr>
</tbody>
</table>

*: Comparison with 3DE, p < 0.01.

Conclusions: For geometrically asymmetric LVs associated with ventricular aneurysms, real-time 3DE can accurately quantify LV volumes.

**1095-144 Elevated Levels of Serum C-Reactive Protein May Predict Prognosis of Patients With Chronic Heart Failure**

Yasuhiro Mitsuoka, Jong-Dae Lee, Hiromasa Shimizu, Hirotoeo Uzui, Takatoshi Yamazaki, Taketori Ueda. First Department of Internal Medicine, Fukuoka Medical University, Fukuoka, Japan

Background: Several circulating neuroendocrine and inflammatory markers have been shown to have a prognostic significance in chronic heart failure (CHF). We evaluated the serum levels of C-reactive protein (CRP) in CHF patients to examine whether serum levels of CRP are correlated with the severity of CHF, circulating levels of pro-inflammatory cytokines or neurohormones.

Methods: Eighty-six Japanese patients with CHF (30 with non-ischemic cardiomyopathy, 28 with ischemic cardiomyopathy and 20 with valvular heart diseases) were included in this study (left ventricular ejection fraction <45%; cardiomyopathy, 28 with ischemic cardiomyopathy and 20 with valvular heart disease). We evaluated the serum levels of CRP in CHF patients to examine whether serum levels of CRP are correlated with the severity of CHF, circulating levels of pro-inflammatory cytokines or neurohormones.

Conclusion: The serum CRP concentrations were significantly higher in CHF than in controls (0.43 ± 0.06 mg/dl vs. 0.05 ± 0.01 mg/dl, p < 0.01). In CHF, serum CRP was increased along with NYHA functional class, and was correlated with circulating level of IL-6 (r = 0.60, p = 0.01), TNFα (r = 0.68, p > 0.01), ANP (r = 0.50, p < 0.01), BNP (r = 0.51, p < 0.01), and NE (r = 0.42, p < 0.03). In stepwise regression analysis, serum CRP emerged as the independent strongest predictor of IL-6 and BNP. In addition, univariate Cox proportional hazards analysis showed that serum level of CRP was also a significant predictor of mortality in this group of patients (p = 0.0022).

Conclusion: Our data indicated that elevated serum CRP was related to the levels of circulating pro-inflammatory cytokines, neurohormones, and mortality of patients with heart failure syndrome.
An Exaggerated Ventilatory Response to Exercise is Related to Abnormal Exercise Hemodynamics in Patients With Chronic Heart Failure

Michèle de guise, Claire E. Snader, Alyce Venditti, James B. Young, Michael S. Lau. Cleveland Clinic Foundation, Cleveland, OH, USA

Background: In congestive heart failure (CHF), an increased ventilatory response to exercise might be a useful marker of cardiac autonomic balance and predicts mortality. Exercise hemodynamics, namely heart rate (HR) and systolic blood pressure (SBP) responses, also predict mortality. We analyzed the impact of VtNco2 on exercise hemodynamics in chronic CHF.

Methods: Metabolic stress tests of 426 consecutive CHF patients (mean age 52 ± 11, 72% male, 42% with hypertension, 30% with coronary disease (CAD), mean LVEF 21 ± 6) in sinus rhythm (none had pacemakers), not taking ACE inhibitors, simvastatin or diuretics; 90% were reviewed. The patient population was divided in quintiles according to VtNco2 at peak exercise. HR and SBP responses were analyzed for each of the first 4 stages of exercise and at peak exercise or a mostoe naugton protocol. HR response was assessed by calculating the proportion of heart rate reserve (HRR) used while SBP response was measured by rise of SBP in nun Hg.

Results: Patients with higher VtNco2 had attenuated HRR used (P < 0.0001) and SBP rise (P < 0.0001) at peak exercise (Figure relates these to VtNco2 quintiles). Similarly, a higher VtNco2 predicted an attenuated SBP response at Stage 1 of exercise (P = 0.001). Even after adjusting for age, gender, CAD, peak VCO2 and other possible confounders, a higher VtNco2 was associated with lower HRR used (P = 0.04) and SBP rise (P < 0.0001) at peak exercise and with a lower SBP response at Stage 1 (P = 0.08).

Conclusion: In patients with chronic CHF, a higher VtNco2 is strongly linked to autonomic imbalance and predicts mortality. Exercise hemodynamics, namely heart rate (HR) and systolic blood pressure (SBP) responses, also predict mortality. We analyzed the impact of VtNco2 on exercise hemodynamics in chronic CHF.

An Increase in Corrected QT Dispersion on Exercise Predicts Sudden Death in Patients With Chronic Heart Failure - A Prospective Study

Hisazaku Ogita, Masafumi Fukunuma, Tsuyoshi Shimonagata, Kazuaki Kumagai, Isakuen Yamada, Yasunori Asano, Aiko Hira, Mitsutoshi Asai, Noritake Hoki. Osaka Prefectural Hospital, Osaka, Japan

Prolonged QT dispersion (QTd) was reported to be related to malignant ventricular arrhythmias in patients with chronic heart failure (CHF). However, little data showed whether heart rate corrected QTd (QTd(R)) on exercise was related to sudden death. Then, we hypothesized that the prolonged QTd(R) would be more sensitive than exercise than at rest in patients with CHF. We prospectively studied 88 CHF patients without atrial fibrillation who were kept ventricular ejection fraction (EF) was less than 40%. QTd(R) was determined by subtracting the shortest corrected QT interval by Bazett’s formula from the longest one in the standard 12-lead ECG before the entry of the study, we calculated QTd(R) at rest (QTd(R)R) and QTd(R) after Master double stress test (QTd(E)) for all study patients. They were divided into two groups based upon QTd(E) > QTd(R) (Group 1, n = 42) or not (Group 2, n = 46) and were followed up for three years. During the follow-up period of 1-36 months, seven patients died suddenly (six in Group 1 and one in Group 2). There were no significant differences in age, sex, EF, NYHA classification. Kaplan-Meier analysis revealed that the rate of sudden death in Group 1 was significantly higher than that in Group 2 (P = 0.038) (Fig.). These results suggest that an increase in QTd by exercise might be a potent predictive implication for sudden death in patients with CHF.

Going... Going... Gone! The Relationship Between Atrial Fibrillation Duration and Atrial Stunned

Jeanne M. DeCara, Simon Dubeau, Rodney H. Fallow. Boston Medical Center, Boston, MA, USA

Background: Previous investigators have shown that AF of brief (<2 wks) duration is associated with less atrial mechanical dysfunction post-cardioversion (CV) than prolonged AF (>2 wks). The point at which the relationship between AF duration and atrial stunning ceases is unknown. We therefore sought to better define the duration of AF after which the degree of post-CV atrial stunning remains constant.

Methods and Results: Doppler A-wave velocity was measured within 24 hrs of CV in 170 patients with AF of 3-6 months duration. Regression analysis was performed starting with patients with AF 2-4 weeks in duration and was repeated as the patient group was expanded in 1 week increments to include those with longer AF duration. An inverse relationship between AF (weeks) 2-4 4-6 6-8 8-10 n 15 24 24 16 r value -0.524 -0.103 -0.090 -0.341 p value 0.03 0.51 0.66 0.20
pre-CV AF duration and post-CV peak A wave velocity was found. Though this association was statically significant for AF durations up to 9 weeks, further regression analyses in 2 weeks blocks proved that the apparent relationship was entirely driven by a strong correlation in patients with AF of >2 weeks duration.

Conclusions: Contrary to prior belief, the effect of pre-cardioversion AF duration on post-cardioversion atrial stunning persists even after 2 weeks of antithrombotic therapy. However, this effect rapidly dissipates by one month, after which the degree of atrial stunning remains constant.

POSTER

1096
Clinical Aspects of Hypertrophic Cardiomyopathy
Monday, March 13, 2000, Noon-2:00 p.m.
Anaheim Convention Center, Hall A
Presentation Hour: 1:00 p.m.-2:00 p.m.

1096-151 Age Related Acute Results of Percutaneous Septal Ablation in Hypertrophic Obstructive Cardiomyopathy
Hubert Seggewiss, Lothar Faber, Peer Ziemssen, Werner Meyners, Leon Krater, Axel Meissner, Juergen Schlichting. Dept of Cardiology, Heart Center NRW, Ruhr-University Bochum, Bad Oeynhausen, Germany

Background: Elderly pts. with HOCM have outflow tract obstruction (LVOTO) during pharmacological stress, the presence and significance of provokable LVOTO during exercise is poorly understood.

Methods: We compared baseline data and acute results of PTSMA in younger (<40 years), middle aged (40-59 years), and elderly (>60 years) pts. with HOCM who underwent alcohol-induced septal branch occlusion (PTSMA).

Results: Since 1999 241 symptomatic pts. with HOCM were treated.

Group <40 years 40-59 years >60 years

Patients (n) 48 101 91

Women (%) 33 31 62

NYHA (Class)*** 2.5 ± 0.5 2.7 ± 0.5 3.0 ± 0.5

LVOTG at rest (mmHg) 71.9 ± 27.7 69.6 ± 34.7 74.4 ± 39.7

LVOTG >30 mmHg (%) 22.3 ± 3.7 20.5 ± 3.7 20.8 ± 3.8

CMR max. (Uf) 690 ± 310 570 ± 267 525 ± 204

Complications (%) 2 7 1

DDD pacer (%) 2 2

Death (%) 0 0 3.3

Conclusion: Younger pts. show lower LVOTG reduction after PTSMA.

1096-152 Improvement of Acute Results After Percutaneous Transluminal Septal Myocardial Ablation in Hypertrophic Obstructive Cardiomyopathy During Mid-Term Follow-Up
Hubert Seggewiss, Lothar Faber, Peer Ziemssen, Werner Meyners, Leon Krater, Axel Meissner, Juergen Schlichting. Dept of Cardiology, Heart Center NRW, Ruhr-University Bochum, Bad Oeynhausen, Germany

Background: Percutaneous transluminal septal myocardial ablation (PTSMA) by alcohol-induced septal branch occlusion in pts. with HOCM results in acute reduction of left ventricular outflow tract gradients (LVOTG) in >90% of the pts.

Methods: We report on 197 symptomatic pts. (103 men; age 52.1 ± 15.5 years; 9 pts. with prior myectomy, 13 pts. with prior DDD-pacer (PM); NYHA class I-IV) who underwent PTSMA. 2 pts. died 3 weeks (plaque rupture of a preexisting 25% RCA stenosis). During follow-up in 4 pts. SBP at rest. The SBP fall was defined as the maximum SBP in exercise minus the SBP at peak exercise. Each study was then classified as a positive test if a SBP fall greater than x, occurring or the SBP failed to rise by more than y: where x and y refer to SBP cut-off values from 0 to 50 mmHg. True and false positive

Conclusions: Pts. show ongoing symptomatic improvement after PTSMA without significant risk of cardiac complications. Remodeling after circum-

1096-153 Investigation of the Prevalence of Exercise Stress Induced Outflow Tract Obstruction in Hypertrophic Cardiomyopathy
Munnomohan S. Virdee, Yoshitsuka Matsumura, Paul Sorajja, Sanjaya Sharma, Perry M. Elliott, William J. McKenna. St George's Hospital Medical School, London, UK

Background: Although a proportion of patients (pts) with Hypertrophic Cardiomyopathy (HCM) have outflow tract obstruction (LVOTO) during pharmacological stress, the presence and significance of provokable LVOTO during exercise is poorly understood.

Methods: Fifty one pts with HCM were studied (44 ± 14 yrs, 85% male).

Results: Forty two (82%) pts had asymptomatic capitol hypertrophy, the rest concentric hypertrophy. Mean septal thickness was 20 ± 5 mm and atrial size 44 ± 8 mm. There was no difference between supine and erect resting LVOTO (p = 0.21). Twenty seven pts (20% head, 64% chest) had resting LVOTO > 30 mmHg. (61 ± 23 mmHg, Group B). There was no significant difference between groups A and B for age, symptoms, functional class, septal thickness, atrial size and cavity dimensions. In Group A, LVOTO > 30 mmHg developed during exercise in 10 (37%) pts (peak LVOTO 53 ± 28 mmHg, mean rise 34 ± 29 mmHg), with further increases (11-64 mmHg) during recovery in 4 pts. In two pts, LVOTO developed only in recovery (peak LVOTO 33 and 49 mmHg). There was no significant difference between those with and without inducible LVOTO for pattern of hypertrophy (p = 0.8), septal thickness (p = 0.4), atrial size (p = 0.06), resting mitral regurgitation (p = 0.3), symptoms (p = 0.49), NYHA class (p = 0.2), exertional chest pain (p = 1) or exertional pre-syncope (p = 1) in Group A. Patients with inducible LVOTO were more likely to have incomplete SAM (p = 0.006) and an ejection systolic murmur (p = 0.047) at rest. In Group B, resting LVOTO increased by > 10 mmHg in 21 (88%) pts during exercise (mean 28 ± 13 mmHg), and by a further 24 ± 11 mmHg during recovery in 9 pts. In 2 further patients, increases in LVOTO occurred exclusively during recovery (16 and 18 mmHg). The peak gradient during exercise and recovery correlated strongly with resting LVOTO (r = 0.86, p < 0.001).

Conclusions: Significant LVOTO develops in 37% of patients with no roosting LVOTO, and increases in 88% patients with resting LVOTO during exercise. LVOTO provoked during exercise was not, however, associated with greater functional limitation, exertional chest pain or exertional pre-syncope.

1096-154 Delineation of Prognostic Blood Pressure Values for Abnormal Blood Pressure Response to Exercise in Hypertrophic Cardiomyopathy
Paul Sorajja, Perry M. Elliott, Jan Poloniecki, Shaughan Dickie, Munnomohan S. Virdee, Sanjaya Sharma, William J. McKenna. St George's Hospital Medical School, London, UK

Background: Abnormal blood pressure (BP) response to exercise in hypertrophic cardiomyopathy (HCM) is linked to increased risk of sudden death (SD). The precise changes in BP during exercise that are related to SD risk, however, are uncertain. This study aimed to delineate these BP values.

Methods: We examined 247 HCM patients aged <40 yrs who underwent maximal exercise testing on exercise bicycle. Patients with conduction semi-darone (n = 22) were excluded. For each exercise study, the systolic blood pressure (SBP) rise was defined as the maximum SBP in exercise minus the SBP at rest. The SBP fall was defined as the maximum SBP in exercise minus the SBP at peak exercise. Each study was then classified as a positive test if a SBP fall greater than x occurred or the SBP failed to rise by more than y, where x and y refer to SBP cut-off values from 0 to 50 mmHg. True and false positive
rates for each x-y combination were examined with respect to the occurrence of SD. During follow-up (96% complete; median = 48 mos), 14 SD's occurred. During follow-up (96% complete; median = 48 mos), 14 SD’s occurred.

**Results:** The presence of a SBP fall > 10 mmHg yielded the greatest positive predictive accuracy for SD occurrence. A failure of the SBP to rise by > 30 mmHg, however, yielded the greatest sensitivity and negative predictive value (NPV). A table of representative SBP fall (x) and rise (y) cut-off values is shown below.

<table>
<thead>
<tr>
<th>x (mmHg)</th>
<th>0</th>
<th>15</th>
<th>30</th>
<th>45</th>
</tr>
</thead>
<tbody>
<tr>
<td>sensitivity</td>
<td>50.0</td>
<td>42.6</td>
<td>28.5</td>
<td>21.7</td>
</tr>
<tr>
<td>NPV</td>
<td>94.7</td>
<td>90.4</td>
<td>94.6</td>
<td>97.9</td>
</tr>
<tr>
<td>LR</td>
<td>1.35</td>
<td>2.54</td>
<td>3.58</td>
<td>7.14</td>
</tr>
<tr>
<td>LR (x,y)</td>
<td>0.33</td>
<td>0.01</td>
<td>0.01</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Conclusions: A range of BP changes during exercise identifies persons with HCM who are at increased risk for SD. The presence of a SBP fall greater than 10 mmHg for exercise suggests an adverse prognosis. The threshold of a SBP rise of less than 30 mmHg for an abnormal exercise test provides the greatest sensitivity and NPV for SD.

**1096-I 551 Variants of Tumor Necrosis Factor-α, Insulin-Like Growth Factor-2, Transforming Growth Factor-β, and Aldosterone Synthase and the Extent of Hypertrophy in Patients With Hypertrophic Cardiomyopathy**

Deng P. Reddy, Do-Sun Lim, Sherif Nagueh, Miguel Quinones, William Zoghbi, Michael Sole, Robert Roberts, Ali J. Marian. Baylor College of Medicine, Houston, Texas, USA

**Background:** Patients with hypertrophic cardiomyopathy (HCM) exhibit variable degrees of left ventricular hypertrophy (LVH). Causal mutations account for a small fraction of the variability of LVH and genetic background plays a major role. We investigated association of variants of 4 genes, implicated in the pathogenesis of HCM, with LVH.

**Methods:** Genotypes were determined by polymerase chain reaction and restriction mapping. Septal thickness (ST), mass index (LVMI) and LVH score (1-10) were calculated from echocardiograms.

**Results:**

<table>
<thead>
<tr>
<th>Tumor necrosis factor (TNF-α)</th>
<th>0</th>
<th>385</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS (n = 46)</td>
<td>9 ± 4.4</td>
<td>141 ± 47.6</td>
</tr>
<tr>
<td>GA (n = 33)</td>
<td>2.0 ± 0.4</td>
<td>133 ± 32.4</td>
</tr>
<tr>
<td>AA (n = 6)</td>
<td>2.0 ± 0.4</td>
<td>190 ± 25.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aldosterone synthase (CYP11B2)</th>
<th>0</th>
<th>385</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT (n = 37)</td>
<td>1.9 ± 0.5</td>
<td>150 ± 42.5</td>
</tr>
<tr>
<td>TC (n = 77)</td>
<td>2.0 ± 0.4</td>
<td>142 ± 57.2</td>
</tr>
<tr>
<td>CC (n = 9)</td>
<td>2.0 ± 0.4</td>
<td>125 ± 50.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Insulin-like growth factor-2 (IGF-2)</th>
<th>0</th>
<th>385</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG (n = 56)</td>
<td>2.0 ± 0.4</td>
<td>142 ± 40.0</td>
</tr>
<tr>
<td>GA (n = 68)</td>
<td>1.9 ± 0.4</td>
<td>139 ± 59.7</td>
</tr>
<tr>
<td>AA (n = 22)</td>
<td>2.0 ± 0.4</td>
<td>140 ± 40.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Transforming growth factor (TGF-β)</th>
<th>0</th>
<th>385</th>
</tr>
</thead>
<tbody>
<tr>
<td>UC (n = 65)</td>
<td>2.0 ± 0.5</td>
<td>142 ± 50.0</td>
</tr>
<tr>
<td>CT (n = 65)</td>
<td>2.0 ± 0.4</td>
<td>138 ± 41.6</td>
</tr>
<tr>
<td>TT (n = 15)</td>
<td>1.9 ± 0.3</td>
<td>133 ± 61.0</td>
</tr>
</tbody>
</table>

LR = likelihood ratio.

Conclusions: A range of BP changes during exercise identifies persons with HCM who are at increased risk for SD. The presence of a SBP fall greater than 10 mmHg for exercise suggests an adverse prognosis. The threshold of a SBP rise of less than 30 mmHg for an abnormal exercise test provides the greatest sensitivity and NPV for SD.

**1096-157 Hemodynamic Determinants of Exercise-Induced Hypotension in Hypertrophic Cardiomyopathy**

Quirino Clampi, Gwendro Bocchio, Anna Violante, Fiero Mangangu, Maria Angela Lisi, Giulia Sical, Carlo Gabriele Tonchetti, Filippo Finizio, Eligio Pozzella, Raffaella Lombardi, Marco Boccalatte, Alberto Cuocolo, Maurizio Chiariello. Department of Clinical Medicine & Cardiac Sciences, Radiological Sciences, "Federico II" University, Naples, Italy

**Background:** Intracardiac pressure (BP) changes during exercise in about 1 of patients (pts) with hypertrophic cardiomyopathy (HCM), and may lead to hemodynamic instability, which is associated with a high incidence of sudden cardiac death. We analyzed the hemodynamics of exercise-induced hypotension.

**Methods:** 43 HCM pts (age 38 ± 14 years, 34 men) and 10 controls (age 37 ± 15 years, 7 men) underwent maximal symptom-limited exercise treadmill, during ambulatory radionuclide monitoring (VEST). Fourteen HCM pts had hypotension (>20 mmHg decrease) during exercise (HypoBP), 24 had normal (<20 mmHg increase) increase in BP (NIBP), the remaining 3 pts had flat BP and were excluded. VEST data were averaged for 1 min.

**Conclusion:** HCM subjects with a functional mutation in the TNF-α promoter have greater LVH than those without (p = 0.024). Thus, TNF-α, but not CYP11B2, TGF-β, and IGF-2 variants, modify the extent of LVH in patients with HCM.

**1096-156 Systolic Anterior Motion Begins at Low Left Ventricular Outflow Tract Velocity in Obstructive Hypertrophic Cardiomyopathy**


**Background:** In obstructive hypertrophic cardiomyopathy (HCM) systolic anterior motion (SAM) of the mitral valve with mitral-septal apposition is the most common cause of outflow obstruction. If SAM were caused predominantly by the Venturi mechanism, high flow velocity in the left ventricular outflow tract should be found at the time of SAM onset. If, however, the velocity were found to be normal, this would support an alternate mechanism.

**Methods:** We studied with echocardiography 25 patients with obstructive HCM who had a mean outflow tract gradient of 82 ± 6 mm Hg. We compared mitral valve M-mode tracings with continuous wave (CW) and pulsed (PW) Doppler tracings recorded on the same study. A total of 96 M-mode, 129 CW and 151 PW Doppler tracings were digitized and analyzed. For each patient we determined the left ventricular outflow tract CW velocity at the time of SAM onset. For each patient we identified the mean mean interval from Q wave to SAM onset from multiple M-mode tracings. Then, CW velocity in the outflow tract was measured at that same time interval following the Q wave.

**Results:** SAM began mean 1 ± 5 msec after Q wave onset, mean CW Doppler velocity in the left ventricular outflow tract at SAM onset was 89 ± 8 cm/sec. In 68% of cases SAM began before onset of CW and PW Doppler left ventricular ejection.

**Conclusions:** SAM begins at normal left ventricular outflow tract velocity. At SAM onset, though Venturi forces are present in the outflow tract, their magnitude is much smaller than previously assumed; the Venturi mechanism cannot explain SAM. This velocity idea, along with shape, orientation and temporal observations, indicate that drag, the pushing force of flow, is the dominant hydrodynamic force that causes SAM.
and analyzed at baseline, at 1, 3, 6 min, and at peak exercise. Left ventricular atrioventricular volume (SV), cardiac output (CO), and posterior wall thickness (PT) were expressed as a percentage of the baseline value.

**Results:** Equivocal (13.5%) and SV, CO (figure) increased significantly during exercise in all groups (p < 0.001); in contrast, there was no similar increase in heart rate and decrease in PR in the 3 groups. HypoBP was younger (p = 0.015), more symptomatic for angina (p = 0.03), and had less left ventricular hypertrophy (p = 0.002), as compared to NIDP.

**Conclusion:** Exercise-induced hypotension in HCM depends on a blunted increase in CO during exercise, and on an impairment in systolic function. This latter may be due to excessive increase in wall stress, consequence of a lesser degree of left ventricular hypertrophy, and/or to exercise-induced ischemia. This hypothesis could explain higher incidence of angina. A peripheral mechanism for exercise hypotension is unlikely because PR did not change.

**1096-158 Gender-Specific Cardiac Phenotypic Differences Detected by Magnetic Resonance Imaging in Hypertrophic Cardiomyopathy Caused by Sarcomeric Gene Mutations**

David Dogig, Glenn Plessio, Andrew Arani, Gahid Mohiddin, Lameh. Fanaanapazir. National Institutes of Health, NHLBI, Bethesda, MD, USA

**Background:** Increased left ventricular mass (LVM) in hypertrophic cardiomyopathy (HCM) is secondary to impaired sarcomeric function. The cardiac phenotype is highly variable even in patients with the identical mutation. Therefore, the normative responses to the molecular defect are probably modified by several underdetermined factors. In most studies the number of men who present with HCM is higher than women. We therefore tested the hypothesis that this is due to gender differences in clinical expression of HCM.

**Methods and Results:** Cardiac Magnetic Resonance Imaging (MRI) and echocardiography (echo) were performed off all drugs in 34 adult patients (aged > 20 years; 16 men) with HCM caused by sarcomeric mutations: actin (n = 2); B-myosin heavy chain (n = 21); titin (n = 7); myosin-binding protein-C (n = 3); myosin light chain (n = 1). LVM and LV volumes (LVEDV, LVESV and LVEDVI, LVEDVI) were indexed to body surface area. Ejection fraction (EF) were lower in men despite higher LVM and hence, lower wall stress, lower stroke volume (SV), cardiac output (CO) and peripheral resistance (PR) were increased in the 3 groups. HypoBP expressed as % of the baseline value.

**Conclusions:** The maximum number of successive ventricular beats and the percentage of pts with NSVT in the TWA+ group were significantly higher than those in the N group (4.0 ± 2.4 vs 2.3 ± 1.5). Among the eight pts with HF, a genetic abnormality was detected in 5 pts (4 pts: mycillin heavy chain, 1 pt: cardiac myosin-binding protein C). TWA was positive in two pts with a genetic abnormality and NSVT.

**ORAL**

**845 Dilated and Hypertrophic Cardiomyopathies: Clinical Aspects**

Monday, March 13, 2000, 2:00 p.m.–3:30 p.m.

**845-1 Heart-Type Fatty Acid Binding Protein: An Important Predictor of Cardiac Events in Heart Failure**

Kimochi Kornamara, Naotaka Ono, Tatsuo Kinutani, Kiyohiro Hirooka, Yoshio Yasumura, Satoshi Nakatani, Masakazu Yamagishi, Kuniyo Miyake, National Cardiovascular Center, Suita, Japan

**Background:** Heart-type cytoplasmatic fatty acid-binding protein (HFABP) has been proposed as an early marker of myocardial infarction. The protein is abundant in myocardial cells and is involved in the uptake, transport and metabolism of fatty acids, HFABP has been found to provide a higher level of accuracy than creatine kinase or myoglobin for early diagnosis of acute myocardial infarction. We tested the clinical importance of HFABP as a marker for long-term cardiovascular prognosis in idiopathic dilated cardiomyopathy (DCM).

**Methods:** We measured serum HFABP by means of enzyme immunoassay in peripHERal venous blood of consecutive 50 patients with DCM. As a control group, HFABP was measured in 76 normal men and women. Clinical courses of DCM were followed by 28 ± 13 months. Primary endpoint included cardiac death.

**Results:** 1) Normal values were distributed according to lognormal distribution and mean ± 2SD was equal to 5.25 ng/mL. 2) There were no differences in age, sex, NYHA class, LV ejection fraction and plasma BNP levels between HFAM and DCM groups. 3) HFABP values affect cardiac significantly in women (p < 0.002).

**Conclusions:** The HFABP was a useful marker for detecting high risk patients for VT and is closely correlated with a family history of sudden death in HCM.

**845-2 Baseline Plasma Levels of Tumor Necrosis Factor-α Predicts Response to Treatment With Pentoxifylline in Patients With Idiopathic Dilated Cardiomyopathy**

Daniel Skudlisky, Karin Siwlz, Anette Bergmanns, Geoffrey Candy, Pinhas Serelis. Heart Failure Research Unit, Department of Cardiology, Barberanath Hospital, Johannesburg, South Africa

**Background:** We have previously reported beneficial effects of pentoxifylline, a xanthine derivative agent known to inhibit the production of TNFα in patients with idiopathic dilated cardiomyopathy. However, the clinical improvement and the increment in the left ventricular ejection fraction are related to the changes in the TNFα levels has not been established.

**Methods:** In a prospective, randomized, double blind, placebo control study we enrolled 48 patients (mean age 57 ± 10 years, 59% male) with idiopathic dilated cardiomyopathy. Patients were randomized to pentoxifylline 400 mg TDs or placebo. All patients received treatment with digoxin, diuretics and ACE inhibitors. Echocardiograms, radionuclide studies and systolic left ventricular determinations were performed at baseline and after 6 months.

**Results:** 5 patients died during the 6 months study period (6 in the placebo group). Patients treated with pentoxifylline, significantly improved the func-
Background: Familial hypertrophic cardiomyopathy (FHC) is characterized by maladaptive left ventricular hypertrophy (LVM) in response to mutations that impair sarcomeric function. Some of these mutations are associated with a good prognosis (group 2); and 17 normal relatives without mutation (controls). BNP correlated with LVM-I but the significance was low (r = 0.29; p = 0.03). Ejection fractions were similar in groups 1 and 2. BNP levels were several fold higher in FHC caused by malignant mutations. Controls had higher levels of TNF-α compared to rest of the patients in that group (7.3 ± 7 vs 3.7 ± 2 pg/ml, p < 0.01). There were no other baseline differences between these two groups.

Methods and Results: Sixteen BNP levels and LV mass (using magnetic resonance imaging), corrected for body surface area (LVM-I), were measured in 53 subjects: 13 patients with FHC caused by 3 mutations associated with a poor prognosis (group 1); 23 patients with FHC caused by 6 mutations associated with a good prognosis (group 2); and 17 normal relatives without mutation (controls). BNP correlated with LVM-I but the significance was low (r = 0.29; p = 0.03). Ejection fractions were similar in groups 1 and 2. BNP levels related to LVM-I in the 3 groups were:

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Age (years)</th>
<th>WTmax (mm)</th>
<th>LVM-I (g/m²)</th>
<th>BNP (pg/ml)</th>
<th>BNP-LVM-I (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>group 1</td>
<td>25 ± 11</td>
<td>20 ± 5°</td>
<td>72 ± 19°</td>
<td>268 ± 500°</td>
<td>3.8 ± 4°</td>
</tr>
<tr>
<td>group 2</td>
<td>28 ± 15</td>
<td>17 ± 7°</td>
<td>54 ± 25°</td>
<td>48 ± 88°</td>
<td>0.8 ± 1°</td>
</tr>
<tr>
<td>controls</td>
<td>23 ± 12</td>
<td>12 ± 3°</td>
<td>54 ± 11°</td>
<td>26 ± 17°</td>
<td>0.5 ± 0.4</td>
</tr>
</tbody>
</table>

WTmax, maximum wall thickness by MRI; °, p < 0.01; *p < 0.05; **p < 0.001 compared to controls; ***p < 0.0001 compared to group 1.

Conclusions: 1) Mutations associated with poor prognosis tended to have higher LVM; 2) Severity of LVM is associated with increased BNP levels but the correlation between BNP levels and LVM is poor; and 3) Importantly, BNP levels were several fold higher in FHC caused by malignant mutations. Further studies are necessary to confirm the intriguing finding that BNP levels may predict adverse outcome in FHC.
ceduras in both groups at rest and arm nitrate study (table). During follow-up, PG tended to increase in both groups. However, no patient showed PG higher than 40 mmHg after myectomy. In ablation group, 5 patients showed PG higher than 40 mmHg at rest after 3 months.

Conclusions: Both caval ablation and myectomy reduce LVOT obstruction significantly in patients with HOCM. While caval ablation is recommended in elderly, follow-up study revealed that myectomy could normalize the PG more often than ablation.

**R47**

**Myocardial and Vascular Dysfunction in Elderly Patients**

Monday, March 13, 2000, 2:00 p.m.–3:30 p.m.
Anahiem Convention Center, Room 304A

**Aortic Densitability is Severely Reduced and Correlates With Exercise Intolerance in Older Patients With Diastolic and Systolic Heart Failure**

W. Gregory Hundley, Stephen N. Dancy Craig A. Hamilton, Kathryn P. Stewart, Timothy K. Morgan, Kerry M. Link, William C. Little, Dalanie W. Kitzman, Departments of Internal Medicine (Cardiology Section) and Radiology at the Wake Forest University Baptist Medical Center, Winston-Salem, NC, USA

**Background:** Elderly patients with heart failure have reduced exercise tolerance and increased left ventricular (LV) mass regardless of whether their LV ejection fraction is reduced or normal. Aortic distensibility and exercise tolerance are reduced with aging, but it is not known if an exaggerated reduction in aortic distensibility may play a role in both exercise intolerance and LV hypertrophy. This suggests that reduced aortic distensibility contributes to their exercise intolerance.

**Methods:** We studied 29 subjects aged ≥60 years: 10 healthy normals (HN), 10 with diastolic heart failure (DHF), and 9 with systolic heart failure (SHF). We measured with magnetic resonance imaging thoracic aortic distensibility and wall thickness, as well as left ventricular mass and ejection fraction; in addition, with bicycle ergometry, we measured maximal exercise capacity (VO_{2max}). To measure LV mass and ejection fraction, multi-slice multi-frame, gradient echo acquisitions (acquired from base to apex of the left ventricle) were performed and values were calculated according to Simpson's rule. Aortic wall thickness was measured with double inversion recovery images that were positioned perpendicular to the ascending aorta approximately 4 cm above the aortic valve. Aortic distensibility was calculated by the standard formula of: (cardiac cycle dependent changes in aortic area)/(pulse pressure). Aortic distensibility correlated with VO_{2max} (r = 0.99, difference = 2 ± 1 mm^2). Femoral artery area increase after the femoral arterial vasodilatory response has not been characterized in elderly subjects or in elderly HF patients and its relationship to exercise capacity in the elderly is unknown.

**Results:** Compared to the HN patients, those with DPH and SHF had negative exercise intolerance, increased LV mass index (DHF: 128 ± 24 vs. HN: 52 ± 10 grams/m^2), and aortic wall thickness (DHF: 3.5 ± 1.3 vs. SHF: 3.6 ± 0.7 vs. HN: 2.9 ± 0.4 mm). Aortic distensibility correlated with VO_{2max} (r = 0.70) & LV hypertrophy (r = 0.45).

**Conclusions:** Aortic distensibility is reduced in elderly patients with heart failure (regardless of etiology) and is strongly related to VO_{2max} and LV hypertrophy. This suggests that reduced aortic distensibility contributes to exercise intolerance and LV hypertrophy in elderly patients with heart failure.

**R47-1**

**Pulse Pressure Rises Exponentially With Age by Longitudinal Analysis**

Susan J. Ziemann, Edward G. Lakatta, Jerome L. Fleig, Gary Gerstenblith, Frances C. O'Connor, Larry J. Brant, Angelo J.-G. Bos. Gerontology Research Center/NA/NIH and the Division of Cardiology, John Hopkins Medical Institutions, Baltimore, Maryland, USA

**Background:** Pulse pressure (PP) is a major risk factor for cardiovascular disease and is described by cross-sectional analyses to increase linearly with age beyond age fifty. Age changes are best described using longitudinal analyses however, and it is unknown whether the PP changes are indeed linear over the adult age span using a longitudinal model. Pulse pressure (PP) is a major risk factor for cardiovascular disease and is described by cross-sectional analyses to increase linearly with age beyond age fifty. Age changes are best described using longitudinal analyses however, and it is unknown whether the PP changes are indeed linear over the adult age span using a longitudinal model.

**Methods:** Longitudinal data were collected from Baltimore Longitudinal Study on Aging participants (1017 males and 572 females, follow-up = 0-38.6 yrs., mean = 6.9), excluding those on vasoactive medications and those with cardiovascular disease including hypertension, Normative aging change in PP were estimated using a mixed-effects linear regression model controlling for gender, body mass index, cholesterol, reported exercise and smoking habits, and diabete. Coxen conditional PP difference were predicted using age at first visit whereas longitudinal PP changes were predicted using follow-up time and as interaction with other variables.

**Results:** The percent change of predicted PP per 10 year follow-up for each starting age decade using cross-sectional (open circles) and longitudinal (solid circles) models are shown in the figure. Beyond age 60, and in contrast to the linear rise in PP predicted by the cross-sectional analysis, an exponential rise in PP is predicted by the longitudinal analysis. The inset depicts mixed-effects estimates of the longitudinal changes in PP by starting age decades and demonstrates that the rate of rise of PP increases with age.
Background: Results of studies in experimental animals have shown that there is an age-related decrease in myocardial fatty acid utilization (MFAU) and an increase in myocardial glucose utilization (MGU). However, it is unknown if this shift in intermediary metabolism occurs in humans.

Methods: Myocardial intermediary metabolism was measured under resting conditions following an overnight fast in 4 healthy young adults (Y: 3 male, 25 ± 6 yrs) and 11 healthy elderly subjects (E: 2 male, 70 ± 5 yrs). No history of diabetes mellitus, hypertension, smoking, or hyperlipidemia; normal rest stress echocardiogram. Measurements of myocardial perfusion (mL/g/min), oxygen consumption (MV02), MFAU and MGU (all in µmol/g/min) were performed by PET with 13C-glucose, 13C-acetate, 13C-palmitate, and 13C-glucose, respectively.

Results: Levels of myocardial perfusion, MV02, plasma glucose and insulin levels (mmol/L) were similar between groups (p = NS for all). Plasma free fatty acid levels tended to be higher in Y than in E (0.86 ± 0.30 vs. 0.58 ± 0.13, p = 0.053). Levels of MFAU/MV02 were higher in Y (0.039 ± 0.008) than in E (0.017 ± 0.004, p = 0.03). Assuming that fatty acids and glucose are the only substrates used by the myocardium, there was a greater contribution of MFAU to overall substrate utilization in Y compared with E (71 ± 7% vs. 35 ± 17%, p = 0.015). Conversely, there was a greater contribution of MGU to overall substrate utilization in Y compared with E (85 ± 17% vs. 59 ± 5%, p = 0.015).

Conclusion: Although differences in the substrate environment may be contributory, it appears that with age there is a decrease in myocardial fatty acid utilization and increased reliance upon glucose as a myocardial energy fuel. This shift in metabolism may provide a partial explanation for the diastolic HF.

Robert Kelly1, Ron McWalter2, Peter Stonebridge2, Hugh Tunstall-Pedoe3, Allan D. Struthers1, 2, Departments of Clinical Pharmacology, 2Medicine, 3Surgery, 2Cardiovascular Epidemiology, University of Dundee, Ninewells Hospital, Dundee, Scotland, UK

Background: Asymptomatic left ventricular dysfunction (LVSDF) is both common and treatable. So we ought to somehow be identifying these patients. A cost-effective way to identify LVSDF patients who would normally be missed might be to screen patients who present with their first non-cardiac vascular episode, i.e., stroke, even peripheral vascular disease (PVD), or a transient ischemic attack (TIA).

Methods: A consecutive series of 180 Stroke, TIA, and PVD patients, aged between 45-86 years, were identified at first non-cardiac presentation. 60 age and sex matched controls were recruited from general practice. Each patient underwent echocardiography to assess left ventricular function. The ejection fraction (LVEF) was calculated using the Modified Simpson's Rule.

Results: 57 (32%) patients had LVEF < 40%, of whom 75% were asymptomatic. 34 (19%) had LVEF < 35%, 10 (5.5%) had LVEF < 30%. Among the control group, 3 patients had LVEF < 40%, of whom 96% were asymptomatic. Pre-screening these patients for LVSDF using major ECG abnormalities: atrial fibrillation or atrial flutter; ischaemic ECG changes, including previous MI and LBBB (23%) identified 82% of LVSDF patients, compared with 66% LVSDF among control patients.

Conclusion: LVSDF is more prevalent among Stroke, TIA, and PVD patients than in the general population. Our data would suggest that there is enough LVSDF in such patients to warrant routine screening. Our data also suggests that such echo screening is likely to be even more cost-effective if it is limited to those patients with major ECG abnormalities.

Poster 3:15 p.m.

ABSTRACTS - Cardiac Function and Heart Failure 193A

Screening for Treatable Left Ventricular Systolic Dysfunction in Stroke, Transient Ischemic Attack, and Peripheral Vascular Disease Patients: A Case-Control Study

Robert Kelly1, Ron McWalter2, Peter Stonebridge2, Hugh Tunstall-Pedoe3, Allan D. Struthers1, 2, Departments of Clinical Pharmacology, 2Medicine, 3Surgery, 2Cardiovascular Epidemiology, University of Dundee, Ninewells Hospital, Dundee, Scotland, UK

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models were constructed from the MR images. End-systolic stress was cal-
culated by FEA with systolic model loads determined by noninvasive Miller
carotid artery pressures.
Results: The global LV/S/L ratio (dynes/cm², × 10³) for all was significantly
higher in ICM patients (chart) at rest (0.45 ± 0.42 vs. 0.33 ± 0.11, p < 0.001)
and with dobutamine (11.8 ± 6.65 vs. 3.28 ± 1.76, p < 0.001). In the regional
analysis (212 LV wall segments) this methodology accurately differentiated
normal from abnormally contracting regions. Comparison to echocardiogra-
phy at rest, demonstrated an 88% sensitivity and 85% specificity (normal
regional ratio defined as mean ± 2SD in the normal volunteers).
Conclusion: n ratio is a sensitive, noninvasive, readily applicable index that may help in the quantitative identification of the dysfunctional areas in ICM.

1115-143 Jugular Venous Pressure Predicts Septal Function and Left Ventricular Performance in Heart Failure
S. Gabrielle Horne, Robert N. Anderson, Christ Koilpillai, David E. Johnstone; University of Calgary, Calgary, Alberta, Canada
Background: In animal models of heart failure (CHF), and CHF patients with
normal conduction, septal function is better preserved than that of the LV
free-wall. We hypothesised that high RV filling pressure would adversely affect
septal systolic function in heart failure through impairment of septal diastolic
loading. To test this, we analysed echocardiographic data from 50 patients
with stable CHF and normal electrical conduction, with and without elevated
JVP.
Methods: LV parasternal short axis end-diastolic and end-systolic frames
were digitized and endocardial borders traced. After correction for systolic
translocation and rotation, a floating central and 32 radial chords were con-
structed. Shortening from end-diastole to end-systole along each chord was
measured.
Results: Patients with elevated JVP (n = 18) and normal JVP (n = 32) had
similar LV end-diastolic areas (41 ± 11 vs 44 ± 9 cm², p = ns) and 5% of patients
with septal infarction on ECG (28 vs 31), but patients with elevated JVP had a
worse NYHA class (3.1 ± 0.2 vs 2.7 ± 0.7), and lower LV stroke area (5 ± 6 vs
8 ± 5 cm²) than those with normal JVP (both p < 0.05). Septal chord shortening
(sum % shortening chords 22–31) was similar to that of the LV freewall (sum
% shortening chords 7–16) in patients with elevated JVP (54 ± 34 vs 69 ±
22%, p = ns), but considerably greater than that of the LV freewall in patients
with normal JVP (147 ± 17 vs 55 ± 16%, p = 0.001). Comparing individual
cords between groups, % shortening of 10 septal chords was significantly
less in patients with elevated JVP compared to those with normal JVP (see figure).

Conclusion: In CHF patients with normal JVP, septal contribution to LV
systolic function is enhanced, but with elevated JVP this is lost, and is as-
associated with a lower index of LV systolic performance and worse functional
class.

1115-144 Subclinical Atherosclerosis Detected by Lumbar Aortic Calcification is an Important Predictor of Congestive Heart Failure
Craig R. Walsh, L. Adrienne Cupples, Daniel Levy, Peter W.F. Wilson,
Christopher J. O’Donnell, NHLBI’s Framingham Heart Study Framingham,
MA, USA
Background: Coronary artery disease is a major cause of congestive heart
failure (CHF). Detection of subclinical extraarterial atherosclerosis may
identify subjects at risk for development of CHF.
Methods: Aortic vascular calcifications seen on lateral lumbar radiographs
were studied as a predictor of CHF over 22 years of follow-up. Films were orig-
inally obtained in 1030 men (mean age 60 years) and 1437 women (mean age
61 years) free of CHF as part of an osteoporosis study conducted in 1968 in
the Framingham Heart Study. Anterior and posterior wall calcific deposits in
the L₁-L₄ region of the aorta were graded according to increasing severity.
Tertiles of lumbar aortic calcification (LAC-range 0-24 points) were defined
after summing the anterior and posterior gradings. Proportional hazard mod-
els were used to test for associations between LAC score and CHF risk in men
and women.
Results: There were 141 cases of CHF in men and 160 cases of CHF in
women. In comparison with the lowest LAC tertile, age-adjusted risk for CHF
was increased in tertile 2 and tertile 3 in both men and women. Risk of CHF
was proportional to extent of LAC, and was not materially altered by a multi-
variable model including age, smoking, diabetes, systolic blood pressure, left
ventricular hypertrophy, body mass index, total and I DL cholesterol (table).

Table. LAC score by JVP score in men and women (multivariable model)

<table>
<thead>
<tr>
<th>LAC score</th>
<th>CHF risk</th>
<th>995 CI</th>
<th>CHF risk</th>
<th>995 CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-16</td>
<td>Referent</td>
<td></td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>17-24</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>25-32</td>
<td>1.4</td>
<td></td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>33-40</td>
<td>1.9</td>
<td></td>
<td>1.9</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: Subclinical atherosclerosis, detected by the presence
of calcification of the lumbar aorta on simple lumbar radiographs, predicts risk
of CHF.

1115-145 Differential Prognostic Value of Neurohumoral Activation in Left Ventricular Dysfunction: Coronary Heart Disease Versus Dilated Cardiomyopathy in 428 Nonselected Patients
T. Kottmann, C. Bergmeier, G. Taubert, T. Kleemann, A. Kikowski,
M. Bangert, D. Napel, D. Saaler*, J. Sanges. Department of Cardiology,
Ludwigshafen; *Institutes of Clinical Chemistry, Ludwigshafen, Germany
Background: Left ventricular dysfunction (LVD) is associated with neurohu-
oral activation. The impact of etiology on the neurohumoral advection is
unknown.
Question: Are there differences in prognostic meaning of various neu-
rohumoral parameters (NP) in patients with coronary heart disease (CHD)
versus dilated cardiomyopathy (DCM)?
Methods: 428 consecutive nonselected patients with ejection fraction (EF)
< 45% were registered. Follow-up time was 488 ± 287 (median 454) days. NP
at discharge were measured. Relationship between mortality were compared
in CHD vs. DCM. Medians of NP were taken as cut-off points. Patients: 78%
male, age 64 ± 11 years. EF 29 ± 9%, Ectopy: 60% CHD, 29% DCM, 11%
other.

Result: Mortality was 23% in CHD and 16% in DCM (p = 0.02).

n = 428

<table>
<thead>
<tr>
<th>Norepinephrine</th>
<th>ANP</th>
<th>Vasopressin</th>
<th>Endothelin</th>
<th>Renin</th>
<th>Alkaline</th>
</tr>
</thead>
<tbody>
<tr>
<td>37%</td>
<td>52%</td>
<td>32%</td>
<td>17%</td>
<td>32%</td>
<td>5%</td>
</tr>
<tr>
<td>37%</td>
<td>52%</td>
<td>32%</td>
<td>17%</td>
<td>32%</td>
<td>5%</td>
</tr>
<tr>
<td>26%</td>
<td>21%</td>
<td>20%</td>
<td>12%</td>
<td>20%</td>
<td>10%</td>
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<tr>
<td>29%</td>
<td>20%</td>
<td>27%</td>
<td>5%</td>
<td>20%</td>
<td>12%</td>
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<tr>
<td>28%</td>
<td>21%</td>
<td>28%</td>
<td>5%</td>
<td>20%</td>
<td>10%</td>
</tr>
<tr>
<td>37%</td>
<td>12%</td>
<td>25%</td>
<td>9%</td>
<td>20%</td>
<td>10%</td>
</tr>
</tbody>
</table>

* p < 0.05

Conclusion: (1) Increased norepinephrine- and ANP-values are associated with higher
mortality in LVD caused by both CHD or DCM.
(2) Vasopressin and endothelin are of large prognostic importance in LVD
caused by DCM but not in CHD.
(3) There is no prognostic value of renin and aldosterone in patients with LVD
caused by both CHD or DCM.

1115-146 A Parameter of Recovery After a Maximal Exercise is an Independent Predictor of Survival in Patients With Left Ventricular Systolic Dysfunction
Pascale De Groote, Valérie Aumégnat, Thibaud Meurice, Olivier Nogue,
Ariane Milinaire, Nicolas Lamblin, Jean-Marc Lablanche. University of Lille,
France
Background: Peak VO₂ is a powerful prognostic parameter in patients (pts)
with congestive heart failure (CHF) but particularly in pts with severe exercise
intolerance (peak VO₂ < 10 ml/min/kg). In order to improve the prognostic
information of the cardiopulmonary exercise test, other parameters must be
defined.
Methods: We prospectively analyzed the kinetics of VO₂ during exercise
and recovery (Post) in 411 consecutive pts with stable CHF (35 women, mean
vo...
We determined the ratio between total VO2 during exercise and during rest (RVEF) were repeated after an i.v. bolus of nitroglycerin (NTG, mean dose 3% was defined as peak VO2 - VO2 at 3 min of rest divided by peak VO2. Survival. Mortality rates in subgroups of pts divided according to %VO2 and complex geometry. We investigated the prognostic significance of visually assessed RV size in a large cohort of patients (n = 2265) with LV ejection fraction (EF) < 40%. Mean age was 68 ± 11 years, mean follow up of 855 days, and there were 743 deaths. RV enlargement (RVE) and EF were visually estimated in 1452 patients. Mild, moderate and severe degrees of RV enlargement (R VE) were present in 554 (24%), 230 (10%) and 59 (2%) of the patients respectively. Presence of moderate or severe RVE was associated with a higher 5 year mortality compared to those with no or mild RVE (80% vs 60%, p = 0.02). Mortality was also a function of the degrees of RVE (p = 0.011). Effect of R VF on mortality was greater in patients with better EF those with atrial fibrillation and in younger individuals.

Conclusions: (1) Visually estimated RV enlargement is a strong predictor of mortality in those with moderate and severe LV dysfunction. (2) Mortality was also a function of the degrees of RV enlargement. (3) The interaction between LV enlargement and mortality is affected by the level of LV systolic function, age and presence or absence of atrial fibrillation.

Effect of Right Ventricular Size on Prognosis in Patients With LV Dysfunction: Results From a Cohort of 2265 Patients With LV Ejection Fraction < 40%

Helme Silvet, Jatin Amin, Sriram Padmanabhan, Ramdas G. Pai, Loma Linda VA Medical Ctr, Loma Linda, CA, USA

The right ventricular (RV) function has been associated with prognosis in relatively small cohorts of patients with heart failure, valvular problems and congenital heart diseases. But, RV function assessment is difficult due to its unique geometry. We investigated the prognostic significance of visually assessed RV size in a large cohort of patients (n = 2265) with LV ejection fraction (EF) < 40%. Mean age was 68 ± 11 years, mean follow up of 855 days, and there were 743 deaths. RV enlargement (RVE) and EF were visually estimated in 1452 patients. Mild, moderate and severe degrees of RV enlargement (RVE) were present in 554 (24%), 230 (10%) and 59 (2%) of the patients respectively. Presence of moderate or severe RVE was associated with a higher 5 year mortality compared to those with no or mild RVE (80% vs 60%, p = 0.02). Mortality was also a function of the degrees of RVE (p = 0.011). Effect of RVEF on mortality was greater in patients with better EF those with atrial fibrillation and in younger individuals.

Conclusions: (1) Visually estimated RV enlargement is a strong predictor of mortality in those with moderate and severe LV dysfunction. (2) Mortality was also a function of the degrees of RV enlargement. (3) The interaction between LV enlargement and mortality is affected by the level of LV systolic function, age and presence or absence of atrial fibrillation.

Evaluation of Flow Mediated Vasodilation in the Upper and Lower Limbs of Patients With Congestive Heart Failure

Rajiv N. Patni, Pierre V. Enevezat, Ilya V. Kaplan, Tim Chang, Thieny H. LaJemtel. Albert Einstein College of Medicine, Bronx, New York, USA

Background: Flow mediated vasodilation is known to be reduced in the brachial and femoral artery in patients with congestive heart failure (CHF). Whether the extent of this reduction is the same in the upper and lower limbs, suggesting a systemic (i.e. enhanced nitrous oxide metabolism) rather than local (i.e. reduced shear stress) mechanism, is currently unknown. Accordingly, flow mediated vasodilation in the brachial and popliteal arteries (following reactive hyperemia) was compared in 20 patients with CHF.

Methods: All patients had similar clinical characteristics (EF < 30%, NYHA II-II, on ACEI, diuretics, digoxin; no history of peripheral vascular disease). Brachial/popliteal artery diameter (BAD and PAD, respectively), heart rate and velocity time integral were determined using 2D/cor Doppler echocardiography at rest and following 1, 2, and 4 minutes of artery occlusion (reactive hyperemia). Brachial/popliteal artery blood flow (BABF and PABF, respectively) and % change in BAD/PAD were then calculated at these time points.

Results: Absolute NTG induced reduction of pulmonary resistance below 3.5 units was not associated with a better outcome. However, the event rate was 22% per year in pts with a baseline RVEF > 30%, 21% per year in pts whose RVEF increased after NTG > 30% and 60% per year in pts whose RVEF did not increase to > 30% (p = 0.003).

Conclusion: These data show that in pts with severe CHF and pulmonary hypertension, a valid risk stratification should include the evaluation of the changes of right ventricular function after acute vasodilator administration.

Elevated Circulating Levels of Tumor Necrosis Factor Correlate With Cardiac Remodeling in Patients With Heart Failure

Hector A. Mata, Dorellynn Lee-Jackson, Pamela D. Samuels, Debbie K. Smith, Alvin S. Blaustein, Douglas L. Mann. Veterans Affairs Medical Center and Baylor College of Medicine, Houston, Texas, USA

Background: Previous experimental heart failure models have invoked a possible role for tumor necrosis factor-alpha (TNF) in the process of cardiac remodeling. However, it is not known whether expression of TNF is involved in the remodeling process affecting human subjects with heart failure. Therefore, the purpose of this study was to investigate whether there was a significant relationship between expression of TNF and cardiac chamber geometry in patients with heart failure.

Methods: We studied 155 patients with mild heart failure (NYHA class I and II), 22 pts with moderate heart failure (NYHA class III-A and IIIB), and 10 pts with severe CHF controls free of cardiovascular disease. We measured plasma TNF and TNF soluble receptor type I and II (TNFR1 and TNFR2) by ELISA. We also obtained 2D echocardiograms on patients and controls, and measured absolute values and values normalized for body surface area (index), of left ventricular end systolic diameter (LVesD), left ventricular end diastolic dimension (LVedD), left atrial diameter (LA).

Results: There were significant correlations between TNF levels and LVesD (r = 0.37, p = 0.00013), LVedD index (r = 0.63, p = 0.000016), LVEDP (r = 0.5, p = 0.000057), LVesD index (r = 0.57, p = 0.00015), LA (r = 0.59, p = 0.000067), LVEDP index (r = 0.59, p = 0.00083). Insofar as the data for TNFR1 and TNFR2 were not normally distributed, analyses were log transformation and non-parametric tests were performed. There were significant correlations between LA and both log-TNFR1 (r = 0.4, p = 0.013) and log-TNFR2 (r = 0.45, p = 0.0038). Similarly, when the untransformed data were examined (Spearmann rank order correlation) there were also significant correlations between LA and both TNFR1 (r = 0.4, p = 0.011) and TNFR2 (r = 0.43, p = 0.0060).

Conclusion: Serum levels of TNF and TNF soluble receptors increase with progressive cardiac remodeling (dilatation) in heart failure patients. While it is not possible to establish a cause and effect relationship, these findings suggest that cytokine expression may play a role in the remodeling process in heart failure. This question is now being addressed in the ongoing randomized stent implant study to the antagonism of cytokines (RPNI-300006).
Cardiogenic Shock/Mechanical Circulatory Assistance

Monday, March 13, 2000, 3:00 p.m.—6:00 p.m.
Anaheim Convention Center, Hall A
Presentation Hour: 4:00 p.m.—5:00 p.m.

1116 Diabetes Mellitus in Cardiogenic Shock Complicating Acute Myocardial Infarction: Report From the SHOCK Registry
Daniele M. Ghidini, Sebastian T. Palermo, Tracey Antenellis, Lynn A. Gieper, Jean Bollard, Maryheen Hosley, Thomas P. Coake, Emma Godfrey, Sonja M. McKinlay, Thierry H. LeJemtel, James N. Slater, Judith S. Hochman, For the SHOCK Investigators, UMDNJ-Robert Wood Johnson Medical School, New Brunswick, New Jersey, USA

The international prospective SHOCK Trial Registry included 1,196 patients (pts.) with cardiogenic shock (CS) complicating acute myocardial infarction (MI). Diabetes mellitus (DM) status was determined in 1,163 pts; 379 (33%) had history of DM. DM pts. were more likely to be female (40% vs. 36%, p < 0.001) and less likely to be Caucasian (77% vs. 85%, p = 0.001). DM pts. had a higher incidence of previous MI (43% vs. 34%), hypertension (66% vs. 47%), CHF (30% vs. 15%), and peripheral vascular disease (29% vs. 13%), all p < 0.002. Mean age was similar (69 ± 12 yr), as were rates of smoking, previous PTCA, and previous CABG. Management for CS was similar for DM and non-DM pts. with regard to intravenous vasopressors and pulmonary artery catheterization, but DM pts. were less likely to receive thrombolysis (28% vs. 37%, p = 0.002) and less likely to undergo attempted revascularization (40% vs. 49%, p < 0.001). PTCA was attempted in 26% DM pts. vs. 32% non-DM, p = 0.174. CABG was attempted in 16% DM pts. vs. 20% non-DM, p = 0.108. Survival in DM pts. undergoing PTCA was 48% vs. 56% in non-DM, p = 0.217. Survival in DM pts. undergoing CABG (including those with primary PTCA attempt) was 68% in DM vs. 64% in non-DM, p = 0.875. Survival benefit in DM pts. selected for PTCA and/or CABG (55% vs. 19% when no revascularization was attempted) was similar to that of non-DM pts. (59% vs. 25%). In-hospital survival was lower for all DM pts. (34% vs. 42%, p = 0.007) and DM remained an independent risk factor for in-hospital mortality after adjustment for patient differences between DM and non-DM (odds ratio 1.4, p < 0.008).

Conclusion: DM is an independent risk factor for in-hospital mortality in cardiogenic shock complicating acute MI, DM pts. who undergo PTCA and/or CABG revascularization derive survival benefits similar to those of non-diabetic patients.

1116-120 Left Ventricular Assist Device Preserves Nitric Oxide Dependent Control of Mitochondrial Respiration in Failing Human Hearts
Seema Mital, R. E. Loke, Linda Addonizio, Mehmet Oz, Thomas H. Hintze, Columbia University College of Physicians and Surgeons, New York, New York; New York Medical College, Valhalla, NY, USA

Background: Ventricular unloading using left ventricular assist devices (LVAD) can improve mitochondrial function in end-stage heart failure. Nitric oxide regulates myocardial oxygen consumption by modulating the activity of the mitochondrial electron transport chain. We investigated the role of nitric oxide in the beneficial effect of LVADs in end-stage heart failure.

Methods: Mitochondrial oxygen consumption was measured in isolated left ventricular myocardium from 26 explanted failing human hearts obtained at the time of heart transplantation using the Clark-type oxygen electrode.

Results: Rate of decrease in oxygen concentration is expressed as percentage of baseline and results of the highest dose are indicated. Bradykinin (10 nM, n=4, p<0.001), angiotensin (10 nM, n=4, p<0.001), and nitroglycerin (2.5 x 10^-5 M) significantly decreased oxygen consumption, whereas L-NAME (10^-4 M, n=4, p<0.001), and nitroglycerin (2.5 x 10^-5 M, n=4, p<0.001) and nitroglycerin (2.5 x 10^-5 M, n=4, p<0.001) significantly attenuated the response to bradykinin, angiotensin and nitroglycerin in both in vitro and in vivo experiments.

Conclusion: Nitric oxide mediated regulation of myocardial oxygen consumption can be pharmacologically modulated with ACE inhibitors, amlodipine and nitroglycerin in failing human hearts. Pretransplant LVAD support potentiates endogenous nitric oxide mediated regulation of mitochondrial respiration and likely facilitates the pharmacological actions of ACE inhibitors, amlodipine.

1116-122 Age Related Outcome for Patients Bridged to Heart Transplantation With HeartMate Left Ventricular Assist Devices
G. Martin Muller, Kyrstyna Malinowska, Christine E. Lawless, Barbara A. Picard, John C. Monde, John A. Robinson, Roque Pifarre, Bryan K. Foy, Mamoosh Bakhos, Loyola University of Chicago Health System, Heart Transplant/Heart Failure Program, Maywood, Illinois, USA

Background: Chronic immunosuppression, allograft coronary disease and decreasing availability of the donor hearts have continued to limit the benefits of the heart transplantation (HT) in patients with the end stage of heart failure in whom HT is deemed the only hope for survival. At the same time, there is a growing number of successfully supported left ventricular assist devices (LVAD) patients surviving and awaiting HT retransplantation longer LVAD implant times. We hypothesized that older patients may not be able to withstand LVAD surgery and prolonged implant times pre and post FIT as younger patients. We would like to predict which age group would benefit the most from the LVAD bridge to HT.

Methods: We reviewed our experience with the pneumatic and vented electric HeartMate left ventricular assist devices (LVAD) implanted in our institution between 6/1992 to 3/31/99. Twenty seven patients were implanted with pneumatic LVADs and twenty eight patients were implanted with electric HeartMate LVADs. Parameters until the time of HT or 1 year follow up was evaluated. The youngest LVAD recipients were 14–50 years old comprised Group I and the older LVAD recipients comprised Group II.

Results:

<table>
<thead>
<tr>
<th>Group</th>
<th>(N = 22)</th>
<th>(N = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality on LVADs prior to HT</td>
<td>2/22 (9.1%)</td>
<td>11/32 (34.4%)*</td>
</tr>
<tr>
<td>1 Year Survival after HT</td>
<td>18/22 (81.8%)</td>
<td>16/22 (68.1%)</td>
</tr>
<tr>
<td>Overall Survival after HT</td>
<td>15/22 (68%)</td>
<td>12/22 (54.5%)</td>
</tr>
<tr>
<td>p</td>
<td>&lt; 0.05</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: The above data demonstrates that older patients had a statistically significant higher mortality while on LVADs. Even if they fortunate enough to receive a donor heart and undergone HT, older patients seen to do worse than younger patients. Frequently at the time of the RFMATCH trial, there should be special emphasis on careful patient selection for implantation of LVAD and special caution and restrained enthusiasm for LVAD as hope for permanent cardiac support in older patients.

1116-123 Cardiogenic Shock After Acute Myocardial Infarction in the Elderly: The Michigan Cooperative Cardiovascular Project Experience
Rajendra H. Mehta, Erik J. Stalhandske, Patricia A. McCargar, Pamela Rustman, Thomas Ruane, Kim A. Eagle, University of Michigan Heart Care Program, Ann Arbor, Michigan, USA

Background: Few data exist on the clinical outcomes of elderly patients with cardiogenic shock complicating acute MI.

Methods: We analyzed 7,874 consecutive patients ≥ 65 years old with acute MI from the Michigan Cooperative Cardiovascular Project. Patients were divided into these groups: A = < 70 yrs, B = 70-85 yrs, and C = ≥ 85 yrs.

Results: (see table, * p < 0.001, LOS = length of stay): Cardiogenic shock occurred in 540 MI patients (6.9%) with the incidence increasing with age (A = 5.4%, B = 7.0%, C = 7.6%). There were no differences in the incidence of diabetes, time to presentation, anterior MI, non-Q MI, or prior MI among 3 groups. Other patients were less likely to smoke (A = 36%, B = 15%, C = 6%, p < 0.001), have prior CABG (A = 16.8%, B = 15%, C = 4.3%, p < 0.001), have prior CABG (A = 16.8%, B = 15%, C = 4.3%, p < 0.001), and had more coronary artery disease (CA = 21%, B = 16%, C = 4%, p < 0.001). There was no significant difference in age, gender, or previous CABG. The p values were not significant when comparing the groups. The percentage of women (A = 50%, B = 51%, C = 59%; p < 0.01) increased with age. Procedural use declined with increasing age (cardiac catheterization, A = 55%, B = 43%, C = 17%, p < 0.001; PTCA, A = 23%, B = 19%, C = 11%, p = 0.024) and CABG (A = 14.7%, B = 12.1%, C = 2.7%, p < 0.001).

Conclusion: There is a similar reduction in flow mediated vasodilation in the upper and lower limbs of patients with CHF. Our data therefore suggest that a systemic rather than a local mechanism is responsible for the reduction in flow mediated vasodilation seen in the skeletal muscle vasculature of patients with CHF.
Conclusions: Increasing age is associated with increasing mortality rates resulting in shorter hospital length of stay in patients with cardiogenic shock unresponsive to medical treatment. Older patients are less likely to undergo invasive procedures. Whether more frequent transfer to tertiary care centers and/or aggressive revascularization in the very elderly would improve outcomes needs further investigation.

1116-124 Intra-Aortic Balloon Counterpulsation in Patients With Cardiogenic Shock: The BENCHMARK Registry Experience
James J. Ferguson, Marc Cohen, Michael F. Miller, Debra L. Joseph, Robert R. Cuffey Jr., Robert Friedman Jr., E. Magnus Ohman. Texas Heart Institute, Houston, Texas, USA

Background: Patients treated with intra-aortic balloon counterpulsation (IAB) for cardiogenic shock (CS) are at high risk for adverse outcomes.

Purpose: To document outcomes and balloon-related complications of modern-day IABC therapy in patients with and without cardiogenic shock.

Methods: The BENCHMARK registry is a prospective series of all patients undergoing IABC at 132 participating institutions. We compared the outcomes (duration of IABC, LOS, mortality) and balloon-related complications (severe bleeding, major limb ischemia, balloon failure) with/without shock as the primary indication for IABC, in patients not undergoing revascularization, patients treated with percutaneous intervention (PCI) only, and patients treated with CABG.

Results:

<table>
<thead>
<tr>
<th>No Revasc</th>
<th>PCI</th>
<th>CABG</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 367)</td>
<td>(n = 2543)</td>
<td>(n = 5707)</td>
</tr>
<tr>
<td>S</td>
<td>No S</td>
<td>S</td>
</tr>
<tr>
<td>Duration of IABC (hours)</td>
<td>68.5</td>
<td>68.5</td>
</tr>
<tr>
<td>LOS (days)</td>
<td>10.2</td>
<td>9.8</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>59%</td>
<td>31%</td>
</tr>
<tr>
<td>Major ischemia</td>
<td>0.7%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2.7%</td>
<td>2.2%</td>
</tr>
</tbody>
</table>

Conclusions: In the modern-day practice of IABC, the in-hospital mortality of cardiogenic shock is approximately 30-40% in CABG and PCI patients, and >50% in patients not undergoing intervention. IABC-related complications are not more frequent in shock patients (p = 0.05).

1116-125 Assessment of Coronary Bypass Flow During Intraaortic Balloon Pumping
Ike H. Walpoth, Linn Spinge, Pascual Bierlat, Ike Kipter, Peter Nedhardt, Franz Eberli, Otto M. Hess, Thierry Carrel. Cardiovascular Surgery, Cardiology and Anaesthesia, University Hospital, Bern, Switzerland

Background: Intraoperative balloon pumping (IABP) has been shown to improve cardiac output and to reduce morbidity and mortality. IABP augments aortic pressure mainly during diastole and improves coronary artery flow. Thus, the aim of the present study was to assess changes in coronary flow with intraaortic balloon pumping.

Methods: Ten male patients (56 ± 12 years) underwent emergency coronary artery bypass surgery. Cardiac hemodynamics were prospectively studied in these patients undergoing IABP using the transit time volume flow technique (CardioMed 4008, Medi-Stim, Norway). Measurements (n = 60) were performed on and off cardiopulmonary bypass with and without IABP.

Results: Cardiac output (CO) determined by the Fick method did not differ significantly (p = NS) between the two inflation volumes (see Fig., y = 0.002 + 0.97x). In a subgroup of 33 pts with BSA ≤ 1.8 m², there is a significant difference in CO determined by TTE between 32 cc and 40 cc inflation volumes (p < 0.05, Table).

<table>
<thead>
<tr>
<th>BSA ≤ 1.8 m²</th>
<th>BSA &gt; 1.8 m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 cc</td>
<td>30 cc</td>
</tr>
<tr>
<td>CO VTI (ml/min)</td>
<td>5.23</td>
</tr>
<tr>
<td>CO Fick (ml/min)</td>
<td>5.24</td>
</tr>
</tbody>
</table>

Conclusions: Overall, smaller IAB inflation volumes do not affect hemodynamic improvement afforded by IABP counterpulsation. However, in patients with smaller BSA, larger inflation volumes may provide improved CO.

1117 Risk Factors and Miscellaneous Problems in the Elderly

Monday, March 13, 2000, 3:00 p.m.—5:00 p.m.
Anaheim Convention Center, Hall A
Presentation Hour: 4:00 p.m.—5:00 p.m.

1117-151 Serum Uric Acid and Risk of Coronary Heart Disease in Older Adults: A 7-Year Prospective Study
Abraham A. Arjyo, Richard Kronmal, John Robbins, Gregory Bufka. For the Cardiovascular Health Study Investigators; Johns Hopkins Hospital, Baltimore, MD, USA

Background: Uric acid is the final breakdown product of purino metabolism in humans. Several epidemiologic studies have suggested that elevated uric acid level predispose to coronary heart disease (CHD). We investigated this relationship among older adults.

POSTER
Methods: In a prospective study of 5,888 elderly (≥65 years) men and women, we assessed the uric acid level in blood samples of 1,419 participants who were free of cardiovascular disease at baseline and followed them for a median of 7 years for the development of CHD.

Results: We used Cox-proportional hazards models to assess the risks associated with each quintile of uric acid, using the first quintile as the reference group. The unadjusted hazard ratios for the development of CHD for the 2nd, 3rd, 4th and 5th quintiles of uric acid were 1.0 (p = 0.94), 1.2 (p = 0.26), 1.4 (p = 0.01), and 1.8 (p = 0.001), respectively. After adjusting for age, gender, total cholesterol, high-density cholesterol, alcohol use, diabetes, physical activity, smoking, and total triglycerides, the hazard ratios were 0.8, 0.7 (p = 0.3), 0.9 (p = 0.6), 1.0 (p = 1.0), and 1.1, (p = 0.5), respectively.

Conclusions: Among apparently healthy older adults, elevated uric acid was not an independent risk factor of CHD. However, it is associated with the measurement of serum uric acid level as a screening tool for CHD in this population.

1117-152 Association of Plasma Homocysteine With Increased Incidence of New Coronary Events in Older Persons

Willibor B. Aranow, Chul Nnn. Mount Sinai School of Medicine, New York, New York, USA

Background: Increased plasma homocysteine has been associated with coronary artery disease.

Methods: We investigated in a prospective study the association of plasma homocysteine and other risk factors with the incidence of new coronary events (CE) (myocardial infarction or sudden cardiac death) in 153 men and 347 women, mean age 81 ± 9 years. Follow-up was 31 ± 6 months.

Results: CE developed in 194 of 500 patients (pts) (39%). Univariate analysis showed that risk factors for new CE were plasma homocysteine (p < 0.001), vitamin E (inverse association) (p < 0.001), folate (inverse association) (p < 0.001), prior coronary disease (p < 0.001), cigarette smoking (p < 0.001), diabetes mellitus (p < 0.001), hypertension (p < 0.001), obesity (p = 0.012), total cholesterol (p < 0.001), high-density lipoprotein (HDL) cholesterol (p < 0.001), and triglycerides (p < 0.002). Stepwise Cox regression analysis showed that significant independent predictors of new CE were age (p = 0.001, risk ratio = 1.041); plasma homocysteine (p < 0.001, risk ratio = 1.033); cigarette smoking (p < 0.001, risk ratio = 2.324), hypertension (p < 0.001, risk ratio = 2.032); diabetes mellitus (p < 0.001, risk ratio = 2.022); total cholesterol (p < 0.001, risk ratio = 1.013); HDL cholesterol (p < 0.001, risk ratio = 0.965); and triglycerides (p = 0.002, risk ratio = 1.004).

Conclusions: Significant independent risk factors for new CE in older persons were age, plasma homocysteine, cigarette smoking, hypertension, diabetes mellitus, total cholesterol, HDL cholesterol (inverse association), and triglycerides.

1117-153 Is Cholesterol Reduction as Effective in the Elderly?

Celia J. Fang, Thomas A. Pearson, Kecia Brown. University of Rochester School of Medicine and Dentistry, Rochester, NY, USA

HMG-CoA reductase inhibitors (statins) have been shown to be effective in prevention of coronary heart disease (CHD) for the elderly at greater risk. However, it is unclear if statins are as effective or if response to statins changes with age. To study this, 7168 patients (pts) were enrolled in the TARGET study and randomly allocated to atorvastatin 10 mg/day (A) or diet only (D) (n=3437) or A alone (n=329) after recruitment by 1236 primary care physicians. The population ranged in ages 18-91 with good representation for all age strata, especially the elderly (n=1686 aged 70+ years). The % change in LDL-C after A + D vs D alone did not vary over age for men and declined with age for D alone in women. However, the % reaching LDL-C goal of the National Cholesterol Education Project (NCEP) declined markedly from the second to the fourth decade and consecutively increased again to the sixth decade. However, the daytime difference constantly decreased with aging. Mean 24-hour HRV and RR-interval as well as their hourly and hourly of the 24-hour were higher in the 20-29 age group than in the three other age groups. No significant difference was found for baroreflex sensitivity in the two older groups. All the age indexed corresponding to the respiratory rate; and the α low-frequency (LF) index reflecting baroreflex sensitivity corresponding to the spectral power of the LF, a new index whose spectral window includes all the power in the [0.03-0.42 Hz]. All three α indexes were higher in the younger age group than in the older groups. No significant difference was found for baroreflex sensitivity in the two older groups. All the α indexes correlated with age (ρ >0.5, p < 0.01); ρ, age; ρ, age. The age was negatively associated only between α and systolic blood pressure (r = 0.37, B = −1.04, p < 0.0001).

Conclusions: Significant independent risk factors for new CE in older persons were age, plasma homocysteine, cigarette smoking, hypertension, diabetes mellitus, total cholesterol, HDL cholesterol (inverse association), and triglycerides.
Association of Atrial Fibrillation and Aortic Atherosclerosis: An Age-Related Phenomenon in the General Population


Background: Recent data suggest that atherosclerosis of the thoracic aorta (ATA) is associated with embolic events in high-risk patients with atrial fibrillation (AF). We hypothesized that ATA and AF has not been evaluated in the general population.

Methods: Transesophageal echocardiography was performed in 581 subjects, a random sample of the Olmsted County population aged >41 years (stratified by age and sex), as part of the SPARC study (Stroke Prevention: Assessment of Risk in a Community). The presence of ATA (any degree of ATA, in any segment of the thoracic aorta) and complex ATA (proluding atheroma > 4 mm in thickness and/or mobile debris or ulceration) was determined in 42 subjects with electrocardiographically-documented AF (AF group), and compared with 539 subjects without AF (non-AF group).

Results: AF subjects were much older than non-AF subjects (61 ± 10 vs 66 ± 13 yrs, P < 0.001) and more commonly hypertensive (67% of AF vs 53% of non-AF subjects, P = 0.077). Gender, diabetes, hypercholesterolemia, and smoking status were similar in both groups (all P values > 0.10). The frequency of ATA (of any degree) was 74% in AF vs 50% in non-AF (P = 0.002). The frequency of complex ATA was 17% in AF vs 7% in non-AF (P = 0.03). The odds ratios for ATA and complex ATA were 2.87 (95% confidence interval [CI] 1.41-5.83, P = 0.004), and 2.71 (CI 1.13-6.52, P = 0.03), respectively, in the AF group vs the non-AF group. Age was a significant predictor of ATA (P < 0.001) and complex ATA (P < 0.001). After adjusting for age, there was no significant difference in the odds of ATA or complex ATA in the AF vs non-AF groups (Pear = 0.13 and P = 0.75, respectively).

Conclusions: AF in the general population is associated with ATA and complex ATA. This association is primarily related to aging, since both AF and ATA are more frequent in the elderly population. The association between AF and ATA suggests that AF, which is primarily a disease of the very elderly, may not only be a direct cause of embolism, but may also serve as a risk marker for high embolic potential due to multiple alternative mechanisms, including ATA.

Secular Trends in Atrial Fibrillation Over Three Decades in 2052 Older Men and Women in Rochester, Minnesota

Teresa S.M. Tsang, George W. Petty, Marion E. Barnes, JoRean D. Sicks, Michael W. O’Fallon, Jacobi F. Whisnant, James D. Belsey, David S. Chen, J. Peter K. J. M. May Clinic, Rochester, MN, USA

Objective: A significant increase in prevalence of atrial fibrillation (AF) was noted in men, but not women, in the Framingham Heart Study from 1960 to 1988. Reasons for the rising trend and gender differences remain unknown. Secular trends in AF and cardiovascular morbidity over a 36-year period in Rochester, MN, were determined.

Methods: The study population comprised the matched control group for a cohort case-control study, ECG evidence of AF and diagnostic confirmation of myocardial infarction (MI), congestive heart failure (CHF), valvular heart disease (VHD) and diabetes mellitus (DM) were obtained for all.

Results: An age-related increase in AF was present for both sexes in all time periods. A secular trend of increasing AF was identified for men and women aged 65-84 years, with MI and CHF. No increase in DM was noted for either sex.

Conclusions: AF in the general population is associated with VHD and CHF, and in men > 65 years, with MI and CHF. No increase in DM was noted for either sex.

Ambulatory Norepinephrine Infusion as a New Therapeutic Option in Severe Autonomic Orthostatic Hypotension

Olaf Oldenburg, Andreas Kibbeler¹, Stefan Sack, Robert Seng, Thomas Philip¹, Raimund Ebel, University Hospital, Dept. of Cardiology; ¹ Dept. of Nephrology and Hypertension, Essen, Germany

Recurrent syncopees and severe orthostatic hypotension is the key problem in advanced Shy-Drager- (SDS) and Bradbury-Eggleston-Syndromes (BES). Immobilization of patients can be the result of this orthostatic hypotension (OH). Oral antihypertensive therapy often fails in treatment of these patients. Aim of this study was the investigation of an ambulatory norepinephrine infusion therapy in these cases.

Methods: we investigated 10 patients with therapy refractory syn (2-41 years), 5 patients with SDS and 3 with BES. Beside of an oral antihypertensive therapy, 4 patients were bedridden b/o OH and 2 were unable to stay in an upright position for more than 3 min. In all patients syncope occurred in less than 15 min during tilt table testing (60° angulation). After a dose-finding study with i. v. application of norepinephrine, a port-a-cath system was implanted. Using a PCA-pump (Patient Controlled Anaesthesia), norepinephrine was infused in a dosage of 10 to 30 ng/kg body weight. Every patient was individually instructed to use the system.

Results: During continuous blood pressure and heart rate control, all patients were mobilized and tolerated a 45 min tilt table test without any symptoms. Self administration of norepinephrine leads to an almost normal daily life without syncope and dizziness. Today the longest therapy period is 5 years.

Conclusion: In case of therapy refractory, primary autonomic OH, self administrated ambulatory norepinephrine infusion using a porta-cath system in combination with a PCA-Pump, is a safe and welltolerated option.

Platyptea Orthodoxia: Management by Transcatheter Buttoned Device Implantation

P. Syamcsundar Rao, Igor F. Palacios, Richard G. Bach, E.B. Sideris. Saint Louis University School of Medicine, St. Louis, Missouri, USA

Background: Atrial desaturation on upright or sitting position associated with or without prior pneumonectomy in elderly subjects is described as Platyptea Orthodoxia syndrome (POS) and is due to right-to-left shunt across an interatrial communication, usually a patent foramen ovale (PFO). Hitherto, surgical closure of PFO is the only available treatment option. Buttoned device has been used for occlusion of ostium secundum atrial septal defects (ASD), PFOs associated with paradoxical embolism and cerebrovascular accidents and ASD/PFOs in association with other congenital heart defects, causing right-to-left atrial shunt. The objective of this presentation is to describe the use of buttoned device in effectively occluding PFOs, thus relieving hypoxemia associated with POS.

Methods: During a two-year period ending July 1999, seven patients ages, 71 ± 9 (range 89-83) years with POS underwent buttoned device closure of their PFOs.

Results: Echographic and balloon stretched ASD sizes were 8 ± 3 mm and 10 ± 2 mm respectively. The ASD/PFOs were occluded by devices ranging in size from 25 to 35 mm; all had an additional 25 mm occluder placed on the fight atrial side. The oxygen saturation improved (p < 0.001) from 76 ± 7% (range 69-86%) to 95 ± 2% (range 92-98%). No complications were encountered. Symptomatic improvement was seen in all patients. Follow-up of 1 to 24 (median 6) mos revealed persistent relief of symptoms.

Conclusion: Buttoned device closure of PFOs to relieve hypoxemia of POS is feasible, safe and effective and is an excellent alternative to surgical closure.

Effects of Load/Unload Neurohumoral Activation/Blockade on the Failing Heart

Monday, March 13, 2000, 4:00 p.m.-5:30 p.m. Anaheim Convention Center, Room 304A

Improved Responsiveness to Beta-Adrenergic Stimulation in Trabeculae From LVAD Supported Hearts

John D. Madigan, Alessandro Barbone, Mehmet C. Oz, Jeffrey W. Holmes, Daniel Burkhoff. Columbia University, New York, NY, USA

Background: Left ventricular assist device (LVAD) support has been reported to normalize LV chamber geometry, unloaded myocyte shortening, and ex-
preservation of genes for major excitation-contraction coupling proteins. We investigated the effects of LVAD support on the developed force–length curve, force-frequency relationship, and response to $\beta$-adrenergic stimulation in isometrically contracting trabeculae.

**Methods:** At the time of transplantation, trabeculae were dissected from the LV free wall of 5 patients with idiopathic dilated cardiomyopathy and 2 patients supported with an LVAD for 46 and 66 days. The trabeculae were placed in an oxygenated muscle bath at 37°C, stimulated at 1 Hz, allowed to equilibrate for one hour, then prestretched to $L_{max}$. The force frequency relationship was determined at 0.5-Hz steps between 1.0 and 3.0 Hz. Responsiveness to $\beta$-adrenergic stimulation was assessed at 1.0 Hz with a 4 x $10^{-9}$ M dose of isoproterenol.

**Results:** There was no difference in baseline muscle function between LVAD and non-LVAD trabeculae as assessed by the developed force–length curve. (Developed force 12.9 ± 10.4 vs. 9.5 ± 1.6 mmHg at $L_{max}$, $p = 0.49$; 11.52 ± 11.8 vs. 7.0 ± 1.6 mmHg at 95% $L_{max}$, $p = 0.36$). However, both the force-frequency relationship and responsiveness to isoproterenol improved with LVAD support. At $L_{max}$, developed force at 3 Hz was 91 ± 23% and 65 ± 7% of developed force at 1 Hz for LVAD and non-LVAD trabeculae (p = 0.048). At $L_{max}$ and 1 Hz developed force with isoproterenol was 325 ± 49% of baseline for LVAD compared to 157 ± 53% for non-LVAD trabeculae (p = 0.015). Responsiveness within the non-LVAD group depended on the history of isotropic support (developed force 148% with history of dobutamine support, n = 4, vs. 246% without support, n = 1).

**Conclusions:** The most dramatic improvement in muscle function following LVAD support was the increased responsiveness to $\beta$-adrenergic stimulation. The force-frequency relationship also improved significantly, while allometric relationships were not as defined as with the LVAD group reported here. Since LVAD patients did not require isotropic support while on LVAD, the altered $\beta$-adrenergic responsiveness may reflect reversal of derealization rather than direct effects of mechanical unloading. These data suggest that much of the functional improvement observed during LVAD support may be due to recovery of $\beta$-adrenergic pathways. Further, this recovery may be attributable more to decreased requirement for isotropic support during LVAD than to the effects of mechanical unloading.

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**803-3 Mechanical Unloading Versus Neurohumoral Stimulation on Myocardial Structure and Endocrine Function In Vivo**

Ondrej Lisy, Margaret M. Redfield, Sofija Jovanovic, Michaela Jougasaki, Aleksandar Jovanovic, Hanna Leskien, Andre Tericic, John C. Burnett, Jr., Mayo Clinic, Rochester, MN, USA

**Background:** Mechanical load and humoral stimuli such as endothelin (ET) and angiotensin II (ANG II) are potent modulators of cardiac structure and myocardial endocrine function, specifically the gene expression, production and release of the cardiac hormone atrial natriuretic peptide (ANP). While both mechanical load and neurohumoral mechanisms influence cardiomyocyte growth and function, it is unclear which predominates particularly when the heart is unloaded. Our study defines the contribution in vivo of mechanical load as compared to neurohumoral stimulation with a specific focus on myocardial and circulating ET and ANG II during chronic unloading produced by thoracic inferior vena caval constriction (TIVCC), which is characterized by the marked activation of circulating and cardiac ET and ANG II with a reduction in cardiac preload.

**Methods:** TIVCC was produced by banding of the vena cava inferior for 10 days in a group of 7 dogs while in the control group of 6 dogs the band was not constricted (GI IAM). *p < 0.05 vs GI IAM.

**Results:** TIVCC group was characterized by a decrease in CO (2.3 ± 0.2 vs 3.6 ± 0.3, l/min), RAP (−0.7 ± 0.4 vs 3.0 ± 0.4, mmHg) and a decrease in LVVEDD (3.4 ± 0.2 vs 4.0 ± 0.15, cm) compared to the SHAM with a marked activation of ET and ANG II in plasma and in atrial and ventricular myocytes. Despite neurohumoral stimulation the LVMi was decreased in the unloaded hearts compared to neurohumoral stimulation with a specific focus on myocardial and circulating ET and ANG II with a reduction in cardiac preload.

**Conclusion:** These studies provide important insights into the seminal role of myocardial load versus neurohumoral mechanisms in the control of myocardial cell growth and endocrine function in vivo. The chronic mechanical unloading of the heart results in myocardial atrophy and a decrease in ANP synthesis despite marked neurohumoral stimulation.
The aim of this study was to investigate the effects of GH on cardiac function, remodeling and plasma levels of brain natriuretic peptide (BNP) in the early postinfarct phase. Methods: Myocardial infarction (MI) of left ventricular (LV) anterolateral wall was induced by ligation of the left coronary artery in male Sprague-Dawley rats. Three different groups were studied: MI rats treated with GH (GH, n = 12) (2 mg/kg/day), MI rats placebo treated (P, n = 10), and sham operated rats (S, n = 7). All rats were investigated with transthoracic echocardiography at 3 days and 3 weeks after MI. The plasma concentration of BNP was measured using radiomunnoassay after the treatment.

Results: The results are summarized in the table. Treatment with GH attenuated increase in LV volumes and improved LV systolic function. Brain natriuretic peptide (BNP) was increased in P group while treatment with GH normalized the plasma level of BNP.

Conclusions: GH attenuates pathological remodeling and improves LV systolic function without induction of LV hypertrophy. This improvement was associated with normalization of plasma levels of BNP.

ORAL

Dilated and Hypertrophic Cardiomyopathies: Genetic Aspects

Monday, March 13, 2000, 4:00 p.m.-5:30 p.m.
Anaheim Convention Center, Room 213A

855-1 A De Novo Mutation of the Troponin T Gene in a Patient With Hypertrophic Cardiomyopathy

Amanda M. Varnava, Fergus Davison, Leon de Cruz, Fabio Coccolo, Penny M. Elliott, Christina Baboonian, William J. McKenna. St George's Hospital Medical School, London, UK

Background: Mutations in at least 8 genes have been associated with hypertrophic cardiomyopathy (HCM). These mutations are associated with a particularly severe form of HCM characterized by a high incidence of sudden death and a poor overall prognosis, despite inapparent to mild left ventricular hypertrophy. Troponin T mutations have been linked to a particularly severe form of HCM characterized by a high incidence of sudden death and a poor overall prognosis, despite inapparent to mild left ventricular hypertrophy.

Methods: The DNA was extracted from the blood of a 6 year old patient with HCM who had undergone cardiac transplantation. Direct sequencing of exon 8 of the troponin T gene identified a missense mutation at c.277A>G, which resulted in the substitution of the amino acid cysteine for arginine. The mutation was confirmed with restriction digest.

Results: The Arg277Gly mutation was found in the proband, but not in the unaffected parents who underwent DNA haplotyping to confirm genetic parentage, nor in the DNA of 200 normal chromosomes. Pathological examination revealed widespread myocardial disarray (up to 80% of the myocardium).

Conclusion: We present the first de novo mutation of the troponin T gene. This mutation was at a known hot spot and is at an evolutionary conserved site. At histology widespread myocardial disarray was found. This provides the most definitive evidence that mutations of the troponin T gene are indeed a cause of HCM.

4:00 p.m.

855-2 Possible Role of Calcineurin in Etiology of Maladaptive Cardiac Hypertrophy in Familial Hypertrophic Cardiomyopathy Caused by Missense Sarcomeric Mutations

Hae W. Lim, David Bogley, Jeffrey D. Malkowitz, Lameh Fananapazir. Department of Pediatrics, Children’s Hospital Medical Center, University of Cincinnati, and National Institutes of Health, NIH,B1, Bethesda, MD, USA

Background: Familial hypertrophic cardiomyopathy (FHC) is characterized by left ventricular hypertrophy (LVH) and may be caused by mutations in one of several sarcomeric genes. The molecular mechanisms whereby mutations in sarcomeric genes lead to LVH is presently unknown. FHC has been associated with altered intracellular Ca2+ handling which may activate the calcium sensitive phosphatase calcineurin.

Methods and Results: Activated calcineurin levels were quantified by calmodulin co-precipitation followed by Western blotting. To control for variability in the immunoprecipitation procedure and to normalize calcineurin levels, the same blot was probed with actin antibody. Cardiac biopsies were studied from 10 adult patients (LV wall thickness 22 ± 10 mm; range, 17 to 50 mm) with FHC caused by mutations in β-myosin heavy chain (8 patients), myosin binding protein-C (1 patient), and myosin essential light chain (1 patient), as well as from 6 normal controls. Calcineurin levels (mean ± SD; percent of normal values) were significantly higher in FHC patients: 356 ± 169%; range, 127 to 626% greater than controls, p < 0.001. The levels were >250% higher than controls in 8 of the 10 FHC patients. Calcineurin enzymatic activity was measured in 4 of the FHC patients and compared with 4 normal controls. The calcineurin activity (mean ± SE) was significantly greater in the FHC patients 6.42 ± 1.20 pmol/min/mg versus 2.9 ± 0.34 pmol/min/mg in controls, p = 0.0013.

Conclusions: Activated calcineurin may play a role in mediating LVH in FHC. Further studies are indicated to confirm the role of the calcineurin regulatory pathway in FHC and to investigate the potential effectiveness of calcineurin antagonists.

4:30 p.m.
855-5 Histological and Immunohistochemical Myocardial Abnormalities in Early Familial Dilated Cardiomyopathy

Nisal G. Mahon, Aldwyn J. Haven, Mirza K. Baig, Sanjay Sharma, Mark W. Newman, Perry M. Elliott, Brendan M. Madden, Michael J. Davies, William J. McKenna, St George’s Hospital Medical School, London, UK

Background: Left ventricular enlargement (LVE) with preserved systolic function is common in asymptomatic relatives of patients with familial dilated cardiomyopathy (DCM), progresses to overt DCM in a proportion and is postulated to represent early disease. Although inflammation is implicated in the pathogenesis of DCM, studies of human myocardium in early disease are lacking. We performed histological and immunohistochemical (IHC) analysis of endomyocardial biopsies (EMB) of asymptomatic DCM relatives with LVE.

Methods: Expression of class II antigens and ICAM is inversely correlated with fibrosis and likely precedes the development of overt DCM, studies of human myocardium in early disease are lacking. We performed histological and immunohistochemical (IHC) analysis of endomyocardial biopsies (EMB) of asymptomatic DCM relatives with LVE.

Results: A lamin A/C gene mutation associated with dilated cardiomyopathy with variable skeletal muscle involvement

Gary L. Brodsky, Francesco Muntori, Martina R. Di Bartella, Sarejaane Mioce, Gianfranco Smnara, Caroline Srewy, Daniela Tonolo, Liuia Mestroni, CU-CVI, Denver, CO, USA; Imperial College, London, UK

Background: Dilated cardiomyopathy (DCM) is a heart muscle disease characterized by impaired systolic function and ventricular dilatation. Familial transmission of the disease is frequently observed and genetic heterogeneity is indicated by clinical and morphological variability in the disease phenotype. A phenotype recently described is characterized by mild inconstant skeletal muscle involvement in affected family members (MDDC). Cardiomyopathies have been found to be associated with skeletal muscle abnormalities in a number of forms of muscular dystrophy, including limb-girdle and Emery-Dreifuss muscular dystrophy. Mutations in the lamin A/C gene have been shown to segregate with the disease phenotype in five autosomal dominant EDMD families.

Methods: Fourteen family member of a DMD family (MDDC1) underwent family screening. Clinical investigations in affected individuals included endomyocardial biopsy and skeletal muscle biopsy. DNA was obtained from affected and some affected relatives. Genetic analysis included sequencing of the candidate gene lamin A/C, association of the cosegregation of the mutation within the family, and DGGE heteroduplex analysis of 100 control chromosomes.

Results: In family MDDC1, the DCM phenotype was severe and characterized by autosomal dominant pattern of transmission. In addition, the phenotype of affected family members varied from an isolated DCM, to mild limb-girdle, or mild Emery-Dreifuss muscular dystrophy. Coding regions of the lamin A/C gene were PCR amplified from genomic DNA and sequenced. A single nucleotide deletion in exon 6 (p.Ser232del) and all affected individuals were found to be heterozygous for this deletion. The footprint mutation predicts a truncated protein with an altered structure, which abolishes signals critical for the protein assembly and localization. The mutation was not found 100 control chromosomes.

Conclusions: Heterozygosity for a single nucleotide deletion in exon 6 of lamin A/C segregates with the disease in the MDDC1 family. The phenotype heterogeneity observed in this family suggest that lamin A/C mutations can be involved in the pathogenesis of familial DCM, as well as of different forms of muscle dystrophies.
mortality between placebo and bucindolol-treated patients. There was no statistically significant difference in mortality between placebo and bucindolol-treated patients. Conclusion: Full results will be presented.

8:45 a.m.

**803-2 Effect of Metoprolol CR/XL on Time in Hospital and Time Alive Outside Hospital: The MERIT-HF Study**

John Kjekshus, Björn Fagerberg. On behalf of the MERIT-HF Study Group: Oslo University, Oslo, Norway; Göteborg University, Göteborg, Sweden

In the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (BEST, echocardiogram at randomization), 3,961 patients with chronic heart failure in NYHA functional class II-IV and ejection fraction ≤ 0.40 randomized with optimal therapy were enrolled in a double-blind randomized study. Randomization was performed by a two-week single-blind placebo run-in period. The study medication was up-titrated during 6-8 weeks starting with 12.5 mg (NYHA III-IV) or 25 mg once daily (NYHA II). The target dose was 200 mg once daily. Analysis was by intention-to-treat. The mean follow-up time was 1 year.

Altogether 561 patients (29.2%) randomized to metoprolol CR/XL were hospitalized at least once (any cause). The corresponding figure in the placebo group was 668 (33.4%) (risk reduction 18%; p = 0.0043). The corresponding figures for hospitalization due to worsening heart failure was 200 patients (10.1%) and 294 (14.1%), respectively (risk reduction 35%; p = 0.0001). The total number of hospitalizations in the metoprolol CR/XL group (all causes) was 1,021 compared with 1,149 in the placebo group (p = 0.005). Corresponding figures for days in hospital for worsening heart failure was 317 vs 451 days (p < 0.0001). Patients randomized to metoprolol CR/XL spent a total of 10,172 days in hospital (any cause) and patients randomized to placebo a total 12,252 days (p = 0.0048). Corresponding figures for days in hospital for worsening heart failure was 3,401 vs 5,303 days, respectively (p < 0.0001). The mean duration of hospitalization for worsening heart failure was 39% shorter on metoprolol CR/XL as compared with placebo (p < 0.0001). To account for the improved survival on metoprolol CR/XL (145 vs 217 deaths, p = 0.0062 adjusted p = 0.00003 nominal) the number of days spent alive outside hospital was also calculated. Patients randomized to metoprolol CR/XL spent more time alive outside hospital compared with patients randomized to placebo (p = 0.0002).

In patients with symptoms of heart failure and decreased ejection fraction treatment with metoprolol CR/XL decreased the need for hospitalization for worsening heart failure and increased the number of days spent alive outside hospital.

**803-4 Do All Heart Failure Patients Benefit From High Dose Lisinopril? Results From the ATLAS Study**


**Introduction:** In the Assessment of Treatment with Lisinopril and Survival (ATLAS) study in heart failure (CHF) patients, a high 35 mg dose of the ACE inhibitor lisinopril produced a 12% risk reduction (p = 0.002) in the combined endpoint of mortality and hospitalization, compared to a low 5 mg daily dose. Risk reduction for mortality was 8% (p = 0.126). Some patients are at higher cardiovascular risk than others, and might not benefit in the same degree from therapeutic interventions. We investigated whether certain patient subgroups within the mixed ATLAS population had a different response to high dose lisinopril.

**Materials and Methods:** ATLAS was conducted over median 46 months in 3,164 patients with NYHA class II-IV CHF. Cox proportional hazards regression models were used to identify possible interactions between the effect of treatment and clinically-relevant subgroups for both all cause mortality, and the combined endpoint, all cause mortality plus all cause hospitalisation.

**Results:** Age, sex, etiology of CHF, NYHA class, systolic BP and heart rate at entry did not show any interaction with treatment effect. There were no consistent interactions with high or low sodium, potassium or creatinine. Thus these factors did not distinguish subgroups of patients in whom high dose lisinopril was associated with greater or lesser effect compared with the whole ATLAS population. However, there was some evidence that patients taking calcium channel blockers, short acting nitrates or other vasodilators at randomisation might gain less advantage from high dose lisinopril than patients not receiving these medications. High dose lisinopril was well-tolerated in all subgroups.

**Conclusion:** With the possible exception of patients already receiving vasodilators, we have not identified any subgroups of patients in whom the outcome was meaningfully different to the overall study result. Upward dose titration should be attempted in all patients with CHF.

**9:00 a.m.**

**RR3-1 Prevention of Heart Failure by Ramipril in High Risk Patients Without Heart Failure or Systolic Dysfunction**

Selim Yusuf, Malcolm Arnold, James Mathew, James Young, Alvaro Avezum, Victoria Bernstein, Jackie Bosch, Janice Pogue, Linda Richardson, David Johnston. On behalf of the HOPE (Heart Outcomes Prevention Evaluation) Investigators; McMaster University, Hamilton, Canada

**Background:** We evaluated if ramipril, an ACE-inhibitor, as compared to placebo would prevent the development of heart failure (HF) in high risk patients (>55 years, previous vascular disease or diabetes plus one risk factor) without low ejection fraction or prior HF in a double blind randomized trial of 6,015 patients followed for 4-5 years.

**Results:**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Relative Risk</th>
<th>P</th>
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<tbody>
<tr>
<td>Any HF</td>
<td>7.4%</td>
<td>0.78 (0.67-0.90)</td>
</tr>
<tr>
<td>Open label ACE-I</td>
<td>3.3%</td>
<td>0.72 (0.58-0.86)</td>
</tr>
<tr>
<td>For HF</td>
<td>3.2%</td>
<td>0.84 (0.69-1.05)</td>
</tr>
<tr>
<td>CV death + HF Hbp</td>
<td>13.9%</td>
<td>0.77 (0.69-0.86)</td>
</tr>
<tr>
<td>CV death + HF HtoP</td>
<td>10.7%</td>
<td>0.77 (0.69-0.86)</td>
</tr>
</tbody>
</table>

**Conclusion:** Ramipril prevents the development of HF and reduces CV mortality in a broad range of high risk patients without evidence of HF or left ventricular dysfunction.

9:30 a.m.

**803-5 Survival Benefits of Spironolactone Therapy May Be Explained by the Limitation of the Excessive Extracellular Matrix Turnover in Patients With CHF: Insights From the RALES Trial**

Fiaz Zannad, Francois Ali, Brigitte Dousset, Bertram Pitt. On behalf of the RALES Steering Committee and Investigators; Centre d’Investigation Clinique (CIC) INSERM-CHU, Nancy, France

**Background:** In congestive heart failure (CHF), extracellular matrix turnover is a major determinant of cardiac remodeling, diastolic dysfunction and pump capacity. It may be monitored by measuring the serum level of procollagen type III aminoterminal peptide (PIIINP). Animal studies suggested that spironolactone (SPIRO), an aldosterone receptor antagonist may decrease cardiac and vascular fibrosis. Thus, we studied the prognostic significance of PIIINP and its changes during chronic treatment with SPIRO.

**Methods:** A sample of 253 patients from the RALES trial participated in this substudy (CHF NYHA III and IV, mean age 69, LVEF = 26%, ischemic heart disease = 46%, all were on conventional therapy - 76% on ACE inhibitors-). Patients were randomized to placebo or SPIRO 12.5 to 50 mg daily. Serum PIIINP was measured at baseline and 6 months after randomization (radioimmunoassay: 95%CI range in control subjects = 1.7-4.2 μg/l). Mean survival follow up was 24 months. ANOVA and multivariate Cox survival model were used.

**Results:** Baseline serum PIIINP level was a predictor of survival in the SPIRO and placebo group. At 6 months it decreased in the SPIRO: (changes: -17% [5-29] p = 0.005), but not in the placebo group. Baseline levels above the 90th percentile of control levels (>1.2 μg/l) were present in 53% of the patients and were associated with an increased risk of death in the placebo group: (RR = 1.89 [1.12-3.20], p = 0.01). Survival benefit from SPIRO was clustered in those patients with excess mortality related to high baseline PIIINP levels: (RR = 0.54 [0.33-0.86], p < 0.02 vs 1.37 [0.76-2.41], p = 0.29 in low risk patients). Among high risk patients SPIRO nearly suppressed the excess death risk related to high PIIINP level. These findings were unchanged after adjustment for other prognostic factors (NYHA class, serum creatinine and age).

**Conclusion:** In patients with CHF, elevated serum PIIINP was significantly associated with excess mortality. SPIRO decreased serum PIIINP. It is suggested that limitation of the excessive extracellular matrix turnover is a major determinant of the beneficial effect of SPIRO on survival in patients with CHF.
**Abstracts**

**Effects of Vasodilators on Cardiac Output and Hemodynamic Parameters in Patients With Congestive Heart Failure**

Anita Dzauw, Nancy J. Potocnik, Bill G. White, Douglas L. Mann, Baylor College of Medicine, Houston, TX. 4C2 R.Galithensb, MD, USA

**Background:** Vasodilators (VAS) are often used as first-line therapy for the management of heart failure (HF). However, their effects on cardiac output (CO) and hemodynamic parameters are less well characterized.

**Objectives:** The primary objectives were to determine the effects of various vasodilators on CO and hemodynamic parameters in patients with chronic HF.

**Methods:** A total of 100 patients with HF were randomized to receive either nitroglycerin (NTG), hydralazine, or dopamine. Hemodynamic parameters were measured before and after vasodilator administration.

**Results:** Compared to baseline, NTG and hydralazine significantly increased CO, while dopamine had no effect. All vasodilators decreased systemic vascular resistance (SVR) and increased cardiac index (CI).

**Conclusions:** Vasodilators have different effects on hemodynamic parameters in patients with HF. Nitroglycerin and hydralazine are effective in increasing CO, while dopamine has no significant effect.

**ORAL 865**

**Which Neurohumoral Mediators Really Control the Extracellular Matrix and Diastolic Function?**

Chari Y. Teramae, Donna M. Meyer, Margaret M. Redfield, Mayo Clinic, Rochester, Minnesota, USA

**Background:** Heart failure (HF) is characterized by systolic and diastolic dysfunction, β-adrenergic hyporesponsiveness and activation of myocardial nitric oxide (NO) and the natriuretic peptides (NP). β-adrenergic hyporesponsiveness is mediated, in part, by NO as NO synthase inhibition enhances β-adrenergic responsiveness. NO and the NP activate soluble guanylate cyclase and share cGMP as a second messenger. Disparate effects on systolic function are controversial. We hypothesized that if the effect of NO or the NP on β-adrenergic responsiveness is NO-independent, then NO synthase inhibition would also affect the β-adrenergic response.

**Methods:** LV function and response to intravenous dobutamine (DOB: 0.01–0.15 µg/kg/min) were assessed during sequential intracoronary (iC) infusion of NO or particulate (NP) guanylate cyclase agonists in patients with chronic HF. LV microtip pressure recording, LV angiography, LV endomyocardial biopsy and echocardiographic LV wall thickness measurement were performed at baseline and following intracoronary infusion of NO or NP agonists.

**Results:** Compared to baseline, LV stroke work (r = 0.41, p = 0.004) and LV compliance (r = 0.43, p = 0.002) were significantly increased following iC infusion of NO or NP agonists. There was no significant change in LV end-diastolic pressure (r = -0.05 vs Group A; p < 0.05 vs Group B).

**Conclusions:** In patients with DCM, a high level of iNOS expression would also affect the β-adrenergic response.
Methods: The effects of ET-1 (0.1, 1, 10 nM) were tested in right atrial muscle strips (n = 7) from patients undergoing CABG surgery and in isolated rabbit papillary muscles (n = 14) (Weibe-Ringer; 1.25 mM CaCl2; 3PC). The papillary muscles were studied in the absence (n = 9) and in the presence (n = 6) of a nonselective endothelin ETA2 receptor antagonist, PD146065. Isotonic, afterloaded-isotonic and isometric twitches were recorded and analyzed. Parameters for isometric contractions included: resting tension at the beginning (RT0), and at the end (RTend) of the twitch, active tension (AT), peak rates of tension development (+dT/dt) and tension decline (−dT/dt), and time to half relaxation (THR). Only significant results (mean ± SE, p < 0.05) are given, expressed as % baseline.

Results: The figure shows four superposed isometric twitches of a representative papillary muscle. In papillary muscles, ET-1 (10 nM) induced an increase of AT (147 ± 33%), −dT/dt (154 ± 39%) and +dT/dt (145 ± 36%). When compared to control and to RTend, RT0 decreased by 8.2% (0.1 nM), 11 ± 3% (1 nM) and 19 ± 3% (10 nM). This effect was enhanced by afterload being maximum in the isometric twitches. It showed no significant relation with AT. The analysis of atrial strips contractions yielded similar results. All the effects of ET-1 were abolished by PD145065.

Conclusions: ET-1 has a novel effect on the diastolic properties of the myocardium. This response, resting tension, or conversely, increases myocardial diastolic distensibility, when afterload is elevated. It is, therefore, tempting to suggest that ET-1 might contribute to cardiac dilatation when cardiac overload is present (e.g. in heart failure).

Calcineurin Plays a Key Role in Development of Diastolic Heart Failure With Preserved Systolic Function in Hypertensive Rats

Yasushi Sakata, Tohru Masuyama, Kazuhiro Yamamoto, Hiroya Kondo, Masahiro Hori, Keiko Ono, Tsunehiko Kuzuya, Takeshi Miwa, Masatsugu Hori, Osaka University, Suita, Japan

Background: It remains unclear how diastolic heart failure with preserved systolic function (DHF) develops in hypertension. We studied whether calcineurin is involved in the development of DHF by hemodynamic and pathologic observation of hypertensive rats with and without chronic administration of calcineurin inhibitor (FK506: 1 mg/kg/day).

Methods: Sixteen Dahl salt sensitive rats were placed on 8% NaCl diet from 7 wks old. FK was given in 8 rats (group FK(+)). Placenta-derived was given in 8 rats (group FK(-)). Rats fed on 0.3% NaCl diet were defined as control rats (group N, n = 6). Systolic blood pressure (sBP), LV end-diastolic pressure (EDP), LV midwall fractional shortening (MFS), time constant (Tau), LV mass/body weight (LVM) and LV hydroxyproline content (Pro-OH) were measured at 19 wks.

Results: Group sBP (mmHg) EDP (mmHg) MFS (%) Tau (msec) LVM (mg/g) Pro-OH (mmol/g)
N 149 ± 3 8 ± 1 14 ± 1 23 ± 2 2.2 ± 0.1 2.0 ± 0.2
FK(+) 225 ± 2* 14 ± 2* 16 ± 1 30 ± 2* 3.8 ± 0.1* 4.0 ± 0.2* 41 ± 0.2 5.8 ± 0.3
FK(-) 219 ± 5* 6 ± 1* 16 ± 1 24 ± 1* 3.2 ± 0.1* 3.7 ± 0.2*

Data are expressed as mean value ± SEM (*p < 0.05 vs N, †p < 0.05 vs FK(-)).

FK506 administration shortened Tau and increased the elevation of LVEDP in FK(-) without changes in sBP and MFS. In FK(+), LV hypertrophy was significantly milder than in FK(-), but LV fibrosis was not restrained by FK506 administration.

Conclusions: Administration of calcineurin inhibitor attenuated LV hypertrophy and prevented the transition to DHF without any effect on LV threonine in hypertensive rats. Calcineurin may play an important role in the development of DHF, mainly contributing to the development of LV hypertrophy rather than fibrosis.

Ticlopidine Stabilizes the Cardiac Extracellular Matrix. Evidence for a Cyclooxygenase-Mediated Effect

Andreas V. Sigel, Chang-Fu Peng, Erhardt P. Kromer, Gunter A.J. Riegger. Klinik und Poliklinik fur Innere Medizin II, Universitat Regensburg, Germany

Background: Ticlopidine serves as an important tool to prevent subacutestent thrombosis via inhibition of platelet aggregation. In addition, ticlopidine may affect proliferation and collagen synthesis in cardiac fibroblasts, the cellular source for the cardiac extracellular matrix. However, the underlying mechanisms, which are responsible for these effects, are yet unknown.

Methods: We, therefore, treated subcutaneous rabbit cardiac fibroblasts with transforming growth factor beta 1 (TGF-β), the major stimulus for collagen production in the heart, in the presence of therapeutical concentrations of ticlopidine (50 μM) and the cyclooxygenase-inhibitor indomethacin (50 μM).

Results: Ticlopidine significantly increased prostaglandin E2 (PGE2) production by 20% (p < 0.05) but decreased proliferation (−25%, p < 0.05), and decreased mRNA expression by more than 30% (p < 0.05%) in ticlopidine treated cells. Finally, the effects of ticlopidine were blocked when fibroblasts were pretreated with 50 μM indomethacin.

Conclusion: We, therefore, conclude that ticlopidine significantly inhibits cardiac fibroblast proliferation and collagen types I and III production in vitro. The effects of ticlopidine on PGE2 production on one hand and the effects of PGE2 and indomethacin on collagen production on the other, may indicate an involvement of the cyclooxygenase pathway. Finally, given the fact that collagen type I represents the major extracellular matrix protein in the heart, ticlopidine may represent a powerful tool to prevent extracellular remodeling in vivo.
Evolving Concepts Regarding Drug Therapies for Heart Failure I

Tuesday, March 14, 2000, 9:00 a.m.–11:00 a.m.
Anaheim Convention Center, Hall A
Presentation Hour: 10:00 a.m.–11:00 a.m.

1137 Evolving Concepts Regarding Drug Therapies for Heart Failure I

POSTER

1137 Beneficial Effect of Spironolactone on Brain Natriuretic Peptide in Severe Congestive Heart Failure

Michel F. Rousseau, Daniel Duprez, Walter Van Meghern, Annie Roceot, François Van Linden, Sylvie Ahn, Jean Marie Keteleslegers. For the Belgian RALES investigators, University of Louvain, Brussels, Belgium

Background: In the RALES Trial, Spironolactone (S), an aldosterone-receptor blocker, decreased mortality in severe congestive heart failure (CHF).

Methods: To clarify the mechanism of action in a subset of 107 pts (NYHA III–IV, mean ejection fraction 25%), the effect of S (25 mg daily) on the plasma concentration of brain natriuretic peptide (BNP), a neurohormonal marker of left ventricular (LV) function, was assessed at entry (T0) into study, at 3 months (T3) and at 6 months (T6) and the changes compared to the placebo (P) group.

Results: BNP was expressed in pg/mL, geometric mean [95% Cl] and data were compared using a Mann-Whitney-Wilcoxon test.

Moreover, BNP changes from T0 expressed by the ratios T3/T0 and T6/T0 evidenced overtime, compared to the P group, a significant reduction of BNP concentration in the S group (0.99 vs 0.77, p = 0.004 and 0.96 vs 0.77, p = 0.05, respectively).

In conclusion, S decreases significantly the plasma levels of BNP reflecting the beneficial effect of S on the left ventricular remodeling through the reduction of neurohormonal stimulation. This neurohormonal cardioprotection contributes to limit the progression of the disease and to explain the decreased mortality and hospitalizations observed with S in severe CHF.

1137-143 Acute and Long-Term Haemodynamic and Neurohormonal Effects of Candesartan Cilexetil in Patients With Congestive Heart Failure

Veselin Mitrovic, Norbert-Hoff-Kliniken der Max-Pschorz Koesellschaft, Bad Neudhausen, Germany

Background: Candesartan cilexetil (CC) is an AT1 receptor antagonist that produces dose dependent increases in exercise time and improvement of symptoms in congestive heart failure (CHF) patients. The present study investigated haemodynamic, symptomatic and neurohormonal effects (PRA, angiotensin II, aldosterone, ANP, catecholamines) of four dose levels of CC versus placebo in patients with impaired left ventricular function (EF 40%, PCWP 13 mmHg, NYHA Class II/III).

Methods: In a double-blind study, 216 patients were randomised after 2 weeks of placebo run-in to placebo (n = 44) or CC 2 mg (n = 48), 4 mg (n = 46), 6 mg (n = 60) or 16 mg (n = 44) once daily for 12 weeks. 1 hemodynamic measurements over 24 hrs were performed by right heart catheterisation with thermodilution technique after single and multiple doses.

Results: Preliminary results demonstrate single and multiple doses of CC resulted in sustained, statistically significant and dose-dependent reductions in PCWP (primary parameter), PAPmean and SVR (regression analysis). However, no consistent changes in CI were apparent after single or multiple doses of CC or placebo. Significant decreases in aldosterone and ANP, as well as compensatory increases in PRA and angiotensin II were dose-dependent. There were also, statistically significant differences for CC versus placebo for CHF symptom scores (visual analogue scale) in categories "breathlessness" and "relaxation". CC was well tolerated up to a dose of 16 mg once daily with no excess versus placebo nor dose dependency for serious adverse events.

Conclusion: Haemodynamic, symptomatic and neurohormonal effects in the present study demonstrated a consistent beneficial, dose-dependent effect of CC in CHF patients.

1137-144 Plasma Atrial Natriuretic Peptide, Cyclic Guanosine Monophosphate, and Endothelin Response to Omapatrilat in Heart Failure

John B. Kostis, Marc Klagholz, Ole Vestergren, Carol L. Delaney, Wei-chi Liao. UMNJ/Robert Wood Johnson Medical School and New Jersey Medical School, New Brunswick and Newark, New Jersey; Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, New Jersey, USA

Background: Plasma levels of atrial natriuretic peptide (ANP), cyclic guanosine monophosphate (cGMP), and endothelin (ET-1) were increased in patients with severe congestive heart failure. Omapatrilat, a novel vasopeptidase inhibitor (VPI), simultaneously inhibits neutral endopeptidase and angiotensin converting enzyme (ACE). Effects of omapatrilat on ANP, cGMP, and ET-1 were examined in patients with mild/moderate congestive heart failure.

Methods: Fifteen New York Heart Association class III/IV heart failure patients (mean ± SD left ventricular ejection fraction [LVEF] 25 ± 10%) and 12 controls (LVEF 61 ± 6%) received a single oral dose of omapatrilat 25 mg after a 1-month washout period from ACE inhibitors. Plasma concentrations of ANP, cGMP, endothelin-1 and ACE activity were measured at baseline and 4 hours after dose. Data (mean ± SD) are presented.

Results: Plasma ANP and cGMP concentrations increased and ACE activity decreased after omapatrilat dose in both heart failure and control patients; plasma ENDO concentration did not change (see table).

Conclusion: Omapatrilat increased the vasodilator ANP and its second messenger, cGMP, by 20% and 30%, respectively, reflecting vasopeptidase inhibition. Omapatrilat did not affect levels of the vasoconstrictor endothelin in normals or mild to moderate heart failure patients.

1137-145 Combination Therapy With Metoprolol and Felodipine in Comparison to Metoprolol Alone on Top of the Standard Medication in Severe Dilated Cardiomyopathy - A Randomized, Double Blind and Placebo Controlled Study

Frank Edelmann, Markus Knapp, Gregor Simonis, Martin Braun, Carsten Schwencke, Christof Weinbrunner, Matthias Borst, Ruth H. Strasser. Department of Cardiology, University of Heidelberg, Germany

Background: Long term β-blocker therapy with drugs such as Metoprolol has been shown to improve hemodynamics and survival in patients with CHF. In contrast, only a few calcium antagonists such as the high vascular selective agent Felodipine promoted beneficial effects in chronic therapy of CHF. However, with these drugs a slight reflectory sympathetic activation might impair their efficiency in long term treatment. To evaluate it a combination of Metoprolol with Felodipine might improve the hemodynamic response the following study was designed:

Methods: 44 patients (CCMP, LVEF < 40%), stable on standard medication (digoxin, diuretics, ACE-4), were prospectively treated in a randomized, double blind an placebo controlled study with Metoprolol (up to 100 mg/d) combined with Felodipine (up to 10 mg/d). MF n = 15 or with Metoprolol and Placebo, MP n = 16, the third group was on double Placebo, PP n = 13. At baseline and after six months echocardiography and exercise testing was performed. Exercise hemodynamics were evaluated using right heart catheterisation (aortic pressure extremes) and maximal oxygen uptake was measured during treadmill exercise.

Results: The EF increased after 6 months significantly (p < 0.05) only in the MF group (27% to 36%), the other groups showed only minor changes. I hemodynamics at rest and during exercise were significantly improved only under MP therapy (CVP -28%, SVRI +8%, SVI +13%, SVI +13%, SVI +13%, SVI +13%, SVI +13%).

Conclusion: A marked improvement of resting and exercise variables occurred only under Metoprolol. Furthermore, the beneficial effects are blunted by the addition of Felodipine. These data suggest that a combined therapy with β-blockers and calcium antagonists is not advantageous in CHF.
**1137-146**

**Tolerability and Side-Effect Profile of Beta Blockers in Patients With Heart Failure: Differences Between Clinical Trial and Practice Setting**

Ghazanfar Khadim, Javed Butler, Don B. Chomsky, John R. Wilson. Vanderbilt University, Nashville, TN, USA

**Background:** Recent trials have shown survival benefits with beta blockers (BB) in patients with heart failure (HF). These trials included a select group of patients and BB were well tolerated. Side effects profile in general population of HF patients remains unknown. The purpose of the current study was to assess the side effect profile and discontinuation rate of BB and compare it with clinical trials, and compare the side effects profile of metoprolol with carvedilol.

**Methods:** All patients with HF and ejection fraction of <40% started on BB during 6/98 to 12/96 were included in the study. A total of 150 encounters with BB on 107 patients were studied.

**Results:** The mean age of the study population was 54 ± 11 yr., with predominately class II-II symptoms. Mean EF was 24 ± 8%.

**Common Side Effects**

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>VUMC (%)</th>
<th>Carvedilol (%)</th>
<th>Carvedilol (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>65</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>35</td>
<td>33</td>
<td>27</td>
</tr>
<tr>
<td>Hypotension</td>
<td>22</td>
<td>09</td>
<td>22</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>17</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

**Concluded Side Effects Leading to Discontinuation**

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Fatigue</th>
<th>Hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low EF</td>
<td>8</td>
<td>0.7</td>
</tr>
<tr>
<td>Worse HF</td>
<td>2.7</td>
<td>1.6</td>
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</table>

Patients on metoprolol were more likely to complain of impotence and those on carvedilol had more frequent hypotension, nausea and diarrhea. Discontinuation rate for any BB was 26.6% as compared to 5.7% in the US Carvedilol Study. Carvedilol was discontinued in 34% as compared to 20% for metoprolol. All 40 patients intolerant to one BB were switched to another and 3/4 of these were able to tolerate the regimen. Therefore, overall rate of intolerance leading to discontinuation to either of the BB was only 4%.

**Conclusion:** Side effects and discontinuation rate with BB therapy in a general population of patients with HF is much higher than that reported in the clinical trials. However, with appropriate adjustment of BB and other medication dosages, trial with different BB and a close follow-up, most patients can eventually tolerate BB therapy.

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**1137-147**

**Ducindolol Has No Intrinsic Sympathomimetic Activity (ISA) in Nonfailing Human Ventricular Preparations**

J. Sederberg, S.E. Wichman, J. Lindenfeld, E. Woffle, B. Lowes, S. Shaker, R. Roden, M.R. Bristow. Univ Colorado HSC, Denver, CO 80262, USA

Based on data derived from 24 hour Holter-monitored heart rates, hemodynamic effects, adenylyl cyclase (AC) stimulation in membrane preparations and muscles contraction data in isolated tissue preparations we have previously reported that the 3rd generation, low inverse agonist B-blocker bucinolol (B) has no ISA in failing human hearts. Because B has weak ISA in some animal models and because this compound is in clinical development for heart failure we have extended the isolated tissue studies to nonfailing human hearts. Isolated right ventricular (RV) trabeculae of uniform size were dissected free and mounted in 14-16 individual tissue baths at 36°C. Preparations were preincubated with the AC activator forskolin (F) for 15-20 min at a concentration of 10^-6 or 3 x 10^-5 M. Dose-response curves to B or the partial agonist xamoterol (X) were performed in F pretreated trabeculae and compared to trabeculae given F alone preincubation + F+ vehicle for 15-20 min at a concentration of 10^-6 or 3 x 10^-5 M. Dose-response curves to F or X were determined. RVs were divided into those that gave a high (>600 mg) or low maximum tension response to isoproterenol (ISO). The High ISO group included: 3 nonfailing human ventricular hearts and 2 RVs from transplant recipients who had relatively well preserved RV function. Results are in mg ± SEM. *p < 0.05 vs. Low ISO. †p < 0.05 vs. F alone.

**Group**

<table>
<thead>
<tr>
<th>ISO</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>High ISO</td>
<td>207A</td>
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**Conclusions:** 1) We as others have previously reported, F can enhance the efficacy of partial agonists in preparations of human ventricular myotendinous junction. 2) The 3rd generation, low inverse agonist activity of B, detected in Woffle against the F-vehicle control only in High ISO. 3) B has no detectable ISA in High ISO or Low ISO RVs.

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**1137-148**

**Baseline Clinical Parameters Do Not Predict Left Ventricular Ejection Fraction Improvement Following Carvedilol Therapy in Heart Failure**

W.H. Wilson Tang, Umesh N. Khot, Mary S. Larson, Lisa Pirkzaszy, Bob S. Hu, John L. Tan, Michael B. Fowler. Stanford University, Stanford, California, USA

**Background:** Left ventricular ejection fraction (LVEF) may serve as a marker for the benefits seen in large populations treated with β-blockers with improvements in survival and decreased risk of hospitalization. We examined the improvement in LVEF following carvedilol therapy in 266 patients treated for a mean follow-up of 1.7 years (range 0.8–6 years) in order to evaluate predictors of LVEF improvement following carvedilol therapy. We were particularly interested to determine whether an espacly low LVEF (≤20%) predicted a lack of subsequent response or intolerance to carvedilol.

**Methods:** 23% of the 266 patients had serial echocardiographic data before and after carvedilol therapy. Patients were divided into 2 groups based on their LVEF response to carvedilol (≤8% versus >8% units). Various clinical parameters were compared using k and chi-square statistics to determine if they predicted LVEF improvement following carvedilol therapy.

**Results:** Overall, 31 patients (12%) did not complete or did not tolerate carvedilol therapy. Among the 235 patients who received a second bolus of saline or 20 ml VC (2 g), BRs and arterial stiffness were measured after each intervention. BRs was assessed from the ECG and BP (Finapres) using spontaneous sequence analysis. Arterial stiffness was assessed using the SphygmoCor PWV Medical system to give an augmented index (AIX). There was no significant change in AIX from baseline in either group (ΔAIX 2.9 ± 0.6 vs. 1.6 ± 1.2%, p = 0.9).

**Conclusion:** We show a significant improvement in AIX after an intravenous bolus of VC in patients with CHF. VC has been shown to improve endothelial function both acutely and chronically in heart failure. Despite this we did not demonstrate any measurable change in arterial stiffness. It is possible that VC has its beneficial effect through the direct action of a reduction in free radicals on baroreceptor nerve endings. This is supported by a recent study in an animal model showing that free radicals may inhibit baroreceptor firing. This result raises the possibility of a novel therapy to reduce cardiac death in CHF.
Haemochromatosis Gene Mutations in Idiopathic Dilated Cardiomyopathy


Background: Recently 2 mutations [a substitution of cysteine for tyrosine at amino acid 63 (H63D) and a substitution of cysteine for tyrosine at amino acid 282 (C282Y)] have been identified in the hemochromatosis (HH) gene. Since cardiomyopathy is a feature of HH, the frequency of these mutations in idiopathic dilated cardiomyopathy (DCM) was determined.

Methods: Two hundred seven unrelated Caucasian patients with DCM and 200 controls were tested for C282Y and H63D mutations.

Results: 31/207 (15%) DCM v 24/200 (12%) controls carried C282Y [OR1.2 (0.7-2.2)], 74/207 (36%) v53/200 (27%) carried H63D [OR1.6 (1.1-2.5)] and 10/207 (4.8%) v4/200 (2%) were compound heterozygotes (CH) [OR1.9 (0.6-5.6)]. Four DCM and 6 controls were H63D homozygous and 1 DCM was C282Y homozygous. There was a progressive increase in mean serum iron[Fe] and transferrin saturations (TS) from patients with no mutation [median Fe = 16.3 mmol/L, 15-33 mmol/L] through H63D heterozygotes (17.5 mmol/L, 25.8%), C282Y heterozygotes (17.1 mmol/L, 26.6%), H63D homozygotes (20.0 mmol/L, 33.5%), CH (26.8 mmol/L, 41.7%) and C282Y homozygotes (34 mmol/L, 71%). At follow-up (median 80 months) the rate of death or cardiac transplantation was 52/207 (25%). C282Y heterozygotes had less ventricular dilatation [59.9 (± 1.7) mm v 64.9 (± 0.9) mm, p < 0.05], better fractional shortening [24 (± 1.7)% v 18.6 (± 1.4)%], p < 0.01] and a trend towards improved survival free from death or transplantation. [Fe] and TS did not correlate with severity of disease and were not associated with risk of survival.

Conclusion: 1. The frequency of HH mutations is significantly increased in patients with idiopathic DCM. 2. Although C282Y and H63D increase iron levels and transferrin saturationsadditionally, there is no clear relation between iron levels and disease severity or progression. 3. The presence of C282Y is associated with clinically milder disease and a trend towards better survival.
**Results:** Patient age ranged from 55–82 years (mean 66 years); there were 13 men and 3 women. Only 28% of patients survived 4 years after diagnosis (graph: p < 0.0001).

**Methods:** The study group comprised of AL patients awaiting HT who had cardiac arrest. All patients were rhythm monitored. Clinical histories were reviewed for the specific clinical diagnosis (AL or idiopathic dilated cardiomyopathy), details of presentation, findings, pressor dosage, and rhythm abnormalities were recorded. Cardiac arrest was defined as hemodynamic instability requiring cardiopulmonary resuscitation.

**Results:** Of the 22 patients who had monitored cardiac arrest, 9 were male and 3 female. Echocardiography demonstrated findings similar to those previously reported for AL patients including increased ventricular wall thickness, reduced systolic function and decreased rate of ventricular relaxation. The echocardiographic manifestations of AL and ALA are very similar despite cardiac deposition of different amyloid protein substrates. There were no distinctive hemodynamic or morphological features to distinguish AL from ALA. Like AL, evidence of advanced cardiac involvement is associated with poor prognosis.

**Background:** Sudden death is frequent in primary systemic amyloidosis (AL) patients; the mechanism has not been well characterized. We perform heart transplantation (HT) for selected patients with cardiac AL. We reviewed the arrhythmias associated with cardiac arrest in AL patients awaiting HT.

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**Results:** Of the 22 patients who had monitored cardiac arrest, 9 were male and 3 female. Echocardiography demonstrated findings similar to those previously reported for AL patients including increased ventricular wall thickness, reduced systolic function and decreased rate of ventricular relaxation. The echocardiographic manifestations of AL and ALA are very similar despite cardiac deposition of different amyloid protein substrates. There were no distinctive hemodynamic or morphological features to distinguish AL from ALA. Like AL, evidence of advanced cardiac involvement is associated with poor prognosis.

**Background:** Sudden death is frequent in primary systemic amyloidosis (AL) patients; the mechanism has not been well characterized. We perform heart transplantation (HT) for selected patients with cardiac AL. We reviewed the arrhythmias associated with cardiac arrest in AL patients awaiting HT.

**Methods:** The study group comprised of AL patients awaiting HT who had cardiac arrest. All patients were rhythm monitored. Clinical histories were reviewed for the specific clinical diagnosis (AL or idiopathic dilated cardiomyopathy), details of presentation, findings, pressor dosage, and rhythm abnormalities were recorded. Cardiac arrest was defined as hemodynamic instability requiring cardiopulmonary resuscitation.

**Results:** Of the 22 patients who had monitored cardiac arrest, 9 were male and 3 female. Echocardiography demonstrated findings similar to those previously reported for AL patients including increased ventricular wall thickness, reduced systolic function and decreased rate of ventricular relaxation. The echocardiographic manifestations of AL and ALA are very similar despite cardiac deposition of different amyloid protein substrates. There were no distinctive hemodynamic or morphological features to distinguish AL from ALA. Like AL, evidence of advanced cardiac involvement is associated with poor prognosis.
Use of Routine Functional Testing After PTCA was the location of the center at which the pt had their PTCA.

Background: Silent restenosis frequently occurs during the 6 months after angioplasty (ROSETTA) Registry is a prospective multicenter study examining the value of adding two right sided (RV3, RV4) and additional tests at a median of 20 weeks. Univariate and multivariate analyses demonstrated that the chief determinant of the use of routine FT was clinical or procedural characteristics were associated with the routine use of post-PTCA FT, and the primary determinant of the high risk characteristics identified by the ACC/AHA Guidelines were proximal left anterior descending disease, diabetes mellitus.

Methods: In seven out of a series of 34 patients with IVNC we have established the pathological preparations confirmed the echocardiographic findings. Conclusions: Clear-cut diagnostic criteria based on echocardiographic findings are required for the diagnosis of IVNC. The ratio of N/C as measured during endsystole was 3.5 ± 0.8. (3) Demonstration of deep perfused intertrabecular recesses by color Doppler. (4) The predominant localisation of the pathology was mid-lateral (7x), apical (6x) and mid-inferior (6x).

The pathological preparations confirmed the echocardiographic findings.

Conclusions: Close-cut diagnostic criteria based on echocardiographic findings are required for the diagnosis of IVNC. The ratio of N/C as measured during endsystole was 3.5 ± 0.8. (3) Demonstration of deep perfused intertrabecular recesses by color Doppler. (4) The predominant localisation of the pathology was mid-lateral (7x), apical (6x) and mid-inferior (6x).

The pathological preparations confirmed the echocardiographic findings.
Increased Prognostic Value of Body Fat Adjusted with chronic heart failure and for timing the need for cardiac transplantation.

Methods: Consecutive United States Air Force Pilots who underwent symptom-limited exercise testing, thallium scintigraphy, and coronary angiography as part of a standard cardiovascular evaluation (N = 967, age = 43 ± 6, all male, 62% amiloilosa, none with diabetess) were studied. Chronotropic incompetence was defined as a chronotropic index (CRI) of <0.8 and was calculated as (peak heart rate — resting heart rate)/220 — age — resting heart rate, this has been shown to take into account effects of age, resting heart rate, and physical fitness. An impaired heart rate recovery (HRR) was defined as a fall of heart rate during the first two minutes after exercise of <41 beats /minute, this value was calculated by maximizing cre-square values.

Results: Significant coronary disease (CAD), that is at least a 50% lesion of a major vessel, was present in 163 (17%). A low CRI was noted in 65 (7%) when a low HRR was present in 224 (23%); at least one abnormality was present in 301 (31%). A low CRI was strongly associated with CAD (52% vs. 16%, odds ratio [OR] 2.14, 95% CI 1.42–2.56, P < 0.001) as was an abnormal HRR (29% vs. 14%, OR 2.10, 95% CI 1.49–2.99, P < 0.001). After adjusting for age, resting systolic blood pressure and heart rate, smoking status, thrill abnormalities, and the CRI, both a low CRI (adjusted OR 3.35, 95% CI 1.28–4.32, P = 0.006) and an abnormal HRR (adjusted OR 1.52, 95% CI 1.04–2.23, P = 0.031) were independently predictive of CAD. Similarly, the presence of at least one heart rate abnormality was strongly associated with CAD even after accounting for possible confounders (adjusted OR 1.76, 95% CI 1.17–2.64, P = 0.005).

Conclusions: Even after accounting for maximum perfusion abnormalities and other possible confounders, both chronotropic incompetence and an abnormally low heart rate recovery early after exercise are strong and independent predictors of angiographic coronary disease among active Air Force Pilots.

Increased Prognostic Value of Body Fat Adjusted Peak Oxygen Consumption in the Evaluation of Obese Patients With Chronic Heart Failure


Peak oxygen consumption (PKVO2) is used for the risk stratification patients with chronic heart failure and for timing the need for cardiac transplantation. Despite the wide variability in body fat content, this parameter is traditionally expressed as a percentage of total body weight per minute.

Methods: We studied 325 consecutive chronic heart failure patients referred for cardiopulmonary stress testing. 119 patients were categorized as obese (BMI ≥27.8 kg/m²), and ≥27.3 kg/m² in women). Percentage of body fat was measured by the sum of three skinfolds method as described by Jackson and Pollock, and lean body mass (LBM) derived by multiplying the total body weight by [1-% body fat/100]. Mean follow-up duration was 18.8 ± 11.3 months. Baseline clinical, cardiopulmonary parameters as well as outcomes were analyzed for differences between both groups (Table).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Obese n = 119</th>
<th>Non Obese n = 106</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>62 ± 11 vs 58 ± 12.3</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>% fat</td>
<td>29.4 ± 7.5 vs 22.2 ± 5.6</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>AT</td>
<td>11.5 ± 3.7 vs 13 ± 4.3</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>Max VC</td>
<td>20.0 ± 18.4 vs 24.8 ± 23.3</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>PKVO2</td>
<td>14.5 ± 4.8 vs 17 ± 6.4</td>
<td>0.0013</td>
<td></td>
</tr>
<tr>
<td>PKVO2 Lean (Adjusted to LBM)</td>
<td>19.2 ± 6.6 vs 20.9 ± 8.3</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Combined endpoint</td>
<td>11.7 ± 6 vs 18.9 ± 4</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Transient</td>
<td>5.9 ± 6 vs 11%</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

All PKVO2 and AT values are expressed in ml/kg/min.

Results: Whereas PKVO2 and anaerobic threshold (AT) were significantly lower in obese patients, the PKVO2 lean (adjusted to lean body mass) showed no difference. There was a non-significant trend for better outcome in the obese population.

Conclusions: The use of PKVO2 adjusted to lean body mass (PKVO2 Lean) in obese patients with chronic heart failure describes their functional capacity and is a better predictor of clinical outcome.
872-2  Do Hemodynamics Always Predict Survival in Advanced Heart Failure? A Second Look at FIRST (the Flian International Randomized Survival Trial)
Monica R. Shah, Sandra Shimett, Steven McNulty, Kirkwood F. Adams, Jr., Mihai Ghoshniade, Karl Swedberg, Robert M. Califf, Christopher M. O’Connor. Duke Clinical Research Institute, Durham, NC, USA

**Background:** Hemodynamically-tailored therapy with ACE-inhibitors and diuretics may improve morbidity and mortality in patients with advanced heart failure (HF). We reviewed the FIRST database to determine whether tailoring medical therapy independently improved survival, regardless of the drug used in achieving lower filling pressures.

**Methods:** In all, 471 patients with NYHA Class II/III/IV symptoms, ejection fraction (EF) ≤ 25%, cardiac index ≤ 2.2 L/min/m², and pulmonary capillary wedge pressure (PCWP) ≥ 15 mm Hg were randomized to epoprostenol (Epo) or standard care. Baseline hemodynamics were recorded on all patients. In the Epo group, final hemodynamics were recorded after a 24-hour drug titration period. In the control group, baseline measures were used as final hemodynamics, as new drugs were not added. Previous analysis showed higher 1-year mortality with Epo.

**Results:** Overall, patients with a reduction in PCWP of ≤ 9 mm Hg had significantly lower 1-year mortality than those with a reduction of <9 mm Hg, even after adjusting for age, sex, EF, NYHA class, and ischemic etiology (hazard ratio, 0.57; 95% CI, 0.33–0.96; p = 0.04). However, Epo patients with a ≥9 mm Hg reduction in PCWP had 1-year mortality similar to that of the control group (hazard ratio, 0.84; 95% CI, 0.50–1.43; p = 0.529).

**Conclusions:** A reduction in PCWP of ≤ 9 mm Hg may have a positive relationship with survival, but the overall effect of tailored therapy appears linked to the agent chosen to reduce filling pressures. Decreases in PCWP can help guide titration of proven therapies, but the ability of a drug to reduce filling pressures does not guarantee that it will reduce mortality.

872-3  Left Ventricular Hypertrophy Predicts Death and Development of Heart Failure in High Risk Patients without Systolic Dysfunction
James Mathews, Eva Lonn, David Janssone, Jeff Probstfield, Malcolm Arnold, Michael Baird, Kola Danisa, Naiyer Habib, Jackie Bosch, Janice Pogue, Salim Yusuf. For the Heart Outcomes Prevention Evaluation (HOPE) Investigators; McMaster University, Hamilton, Canada; Gainesville Hospital, Gainesville, Illinois, USA

**Background:** The risk of death and cardiovascular morbidity associated with left ventricular hypertrophy (LVH) by electrocardiogram (ECG) in high risk patients is not well documented. Whether LVH by ECG predicts the development of congestive heart failure (CHF) in high risk patients without prior CHF or left ventricular systolic dysfunction is not known.

**Methods:** The HOPE study enrolled 5341 high risk patients (>55 years, previous vascular disease or diabetes plus another risk factor) without prior CHF or left ventricular systolic dysfunction. Total mortality, predefined primary HOPE events (cluster of cardiovascular death, myocardial infarction and stroke) and stroke were analyzed.

**Results:** Cox regression analyses were used to adjust for other possible risk factors. Cox regression analyses were used to adjust for other possible risk factors.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LVH present</th>
<th>LVH absent</th>
<th>p (log rank)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death n (%)</td>
<td>98 (12.4)</td>
<td>696 (7.8%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>CHF n (%)</td>
<td>42 (5.3)</td>
<td>217 (2.3)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Primary events n (%)</td>
<td>124 (15.7)</td>
<td>1076 (12.3)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*First hospitalization for congestive heart failure. **Composite of cardiovascular death, myocardial infarction and stroke.

**Conclusions:** LVH by ECG is a strong, independent predictor of increased risk of death and development of CHF in high risk patients without prior CHF or left ventricular systolic dysfunction.

872-4  The Benefit of Spironolactone in the RALES Trial is Not Primarily Due to a Diuretic Effect
Robert J. Cuddy, Berttram Pitt, Alfonso Perez, Richard Blettman. For the RALES Investigators; University of Michigan, Ann Arbor, Michigan, USA

**Background:** The recent RALES Trial demonstrated a highly significant reduction of the relative risk of mortality in patients with moderate to severe heart failure, when spironolactone (spiro) was added to standard therapy. To determine whether benefit was due to a diuretic effect, we prospectively assessed the sodium retention score (SRS) in a cohort of 198 patients from the overall group of 1663 patients in the trial.

**Methods:** The SRS is based upon evidence of fluid retention, with scores for rales, peripheral edema, hepatomegaly, S3 gallop, jugular venous pulse, and change in body weight. The range of values for the SRS is 1 to 11. Prospective SRS was obtained for spiro (n = 99), or placebo (n = 99) at baseline, and month 1, 2, 3, and 6 following randomization.

**Results:** Survival and hospitalization rates mirrored the overall trial. According to NYHA functional class, the mean SRS was 4.25 for IV, and 2.96 for III patients (p = 0.05). Mean SRS for each treatment group:

<table>
<thead>
<tr>
<th>Baseline</th>
<th>mo1</th>
<th>mo2</th>
<th>mo3</th>
<th>month6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spiro</td>
<td>5.16</td>
<td>2.44</td>
<td>2.45</td>
<td>2.08</td>
</tr>
</tbody>
</table>

Reduction was comparable in both groups, without a significant treatment effect or interaction. For patients with minimally edema (SRS < 3), there was no significant difference between placebo and spiro at baseline, or at any time point through 6 months. In those with greater retention (SRS > 3) mean values were:

<table>
<thead>
<tr>
<th>Baseline</th>
<th>mo1</th>
<th>mo2</th>
<th>mo3</th>
<th>month6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spiro</td>
<td>5.16</td>
<td>2.44</td>
<td>2.45</td>
<td>2.08</td>
</tr>
</tbody>
</table>

Reduction was comparable in both groups, without a significant treatment effect or interaction.

**Conclusion:** Patients in the RALES trial demonstrated mild fluid retention at baseline. There was no treatment effect of spiro on sodium retention (compared to placibo), regardless of baseline severity. These findings indicated that the beneficial effects of spiro were not primarily related to diuresis, and most likely related to other anti-aldosterone effects of spiro. Overall reduction of SRS during follow-up was consistent with comparable clinical management in all randomized patients.

872-5  Clinical Features of Patients with Heart Failure After an Acute Coronary Syndrome: Findings From GUSTO-llb
Monica R. Shah, Maria Cecilia Bahit, Christopher B. Granger, Donald Breyer, Nervina D. White, Eric J. Topol, Robert M. Califf. Duke Clinical Research Institute, Durham, North Carolina, USA

**Background:** The development of heart failure (HF) after an acute ST-segment elevation myocardial infarction (MI) is an established risk factor for mortality. We reviewed the GUSTO-llb database to describe the clinical features of patients who develop heart failure after the entire spectrum of acute coronary syndromes (ACS).

**Methods:** Using the database of GUSTO-llb (n = 12,142), which compared intrudin vs. heparin in ACS, we identified patients who developed HF during the index hospitalization. HF was defined by either pulmonary edema on chest X-ray or at least two of the following: rales ≥ 1/3 of lung fields, dyspnea, use of furosemide, or pulmonary capillary wedge pressure (PCWP) > 18 mm Hg and cardiac index < 2.4 L/min/m².

**Results:** In all, 534 patients (4.4%) developed HF after ACS. Patients who developed HF were older and were more likely to have a history of MI, hypertension, or diabetes. In addition, a higher percentage of women developed HF after compared with men - 197 (5.4%) vs. 337 (4.0%); p = 0.001.

**Conclusion:** Patients who develop HF after ACS are more likely to have a history of MI, hypertension, and diabetes and also are more likely to be...
female. This information can help clinicians predict who will develop HF after ischemic events and institute appropriate therapy early in the course of the event.

**872-6** Prognostic Significance of Manifestations of Acute Congestive Heart Failure: Results from GUSTO Ib Maria Cecilia Bahit, Monica Shah, Christopher Granger, Donald Beasley, Eric Bates, Harvey White, Eric Topol, Robert Califf. Duke Clinical Research Institute, Durham, NC, USA

**Background:** Congestive heart failure (CHF) in the setting of acute coronary syndromes (ACS) is associated with increased mortality. The aim of this study was to identify the prognostic significance of certain signs and symptoms in patients with CHF after ACS.

**Methods:** Using the database of GUSTO Ib (n = 121,422), which compared heparin vs. heparin in patients with ACS, we selected patients who developed congestive heart failure during the index hospitalization. CHF was defined by signs and symptoms of: 1) pulmonary edema on chest X-ray or 2) at least two of the following: dyspnea, respiratory rate > 30/min, jugular venous distension with elevated left atrial pressure, 3) systolic blood pressure < 100 mmHg, 4) PCWP > 18 mmHg and cardiac index (CI) < 2.4 L/min/m², dyspnea, use of furosemide. We examined the relationship of CHF and its manifestations with 30-day mortality using multivariable logistic regression analysis.

**Results:** Of 53,458 patients enrolled CHF within a median time of 2 days. Patients with CHF had higher 30-day mortality than patients without CHF (26.1% vs 9.6%, p < 0.001). In a multivariable model, the significant independent predictors of death, and the percentage of patients with CHF and these features, were:

<table>
<thead>
<tr>
<th>Feature</th>
<th>% of Patients</th>
<th>Odds Ratio CI 95%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxemia</td>
<td>23%</td>
<td>2.25 - 2.08 - 5.15</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Hypotension</td>
<td>12%</td>
<td>1.74 - 1.47 - 2.10</td>
<td>&lt; 0.0015</td>
</tr>
<tr>
<td>Pulmonary Edema</td>
<td>56%</td>
<td>1.18 - 0.95 - 2.28</td>
<td>0.075</td>
</tr>
</tbody>
</table>

After accounting for these three predictors in the multivariable model, the following did not independently predict 30-day mortality: ages > 70, 5 or more concomitant events (p > 0.05) were smoking, angina, ST-segmental depression > 0.2 mV, age at referral, ventricular ectopy, and use of beta-blockers (protective). Results were similar for the MI category, with the exception of angina. In the CABG group, smoking, and in the HHD group, smoking, age and ST depression remained significant.

**Conclusions:** Our data indicate that measured VO₂peak provides valuable additional prognostic information in patients referred for cardiac rehabilitation.

**874** Exercise Testing to Determine Prognosis

**874-1** The Long-Term Predictive Value of Peak Oxygen Intake in 12,109 Men Referred for Cardiac Rehabilitation

Tannvirs Karnawagh, Randall J. Martinz, Larry F. Hamm, Joseph Bayless, Johanna Kennedy, Roy J. Shepherd. Toronto Rehabilitation Centre and University of Toronto, Toronto, Ontario, Canada

**Background:** Understanding factors contributing to cardiac death is important to the risk stratification of patients enrolled in rehabilitation programs. Survival analysis was carried out on data from patients referred to a large outpatient cardiac rehabilitation program.

**Methods:** The study included 12,109 men, aged 55.0 ± 9.6 years, consecutively referred for rehabilitation between 1985 and 1994 who underwent an initial cardiopulmonary exercise test. Using a single-centre observational study design, these patients (7,066 myocardial infarction (MI), 3,077 coronary artery bypass graft surgery (CABG), 1,906 documented ischemic heart disease (IHD)) were followed for a median time of 8.3 years from the time of the test. A Cox proportional hazards model tested factors associated with time to cardiac death in the entire sample and in each of the three diagnostic categories.

**Results:** A total of 1,383 cardiac deaths were recorded during follow-up (11.4% of the original sample). The most powerful predictor of prognosis in all four categories was measured peak oxygen intake (VO₂peak). For the entire sample, VO₂peak values of < 15, 15–22, >22 mL/kg.min⁻¹ resulted in risk ratios of 1.00, 0.70, 0.52 respectively. Other significant indicators (< 0.05) were smoking, angina, ST-segmental depression > 0.2 mV, age at referral, ventricular ectopy, and use of beta-blockers (protective). Results were similar for the MI category, with the exception of angina. In the CABG group, smoking, and in the HHD group, smoking, age and ST depression remained significant.

**Conclusions:** Our data indicate that measured VO₂peak provides valuable additional prognostic information in patients referred for cardiac rehabilitation.

**874-2** Which Patients With Low-Risk Treadmill Scores Need Perfusion Imaging for Risk Stratification?

Irini G. Pronimms, Raymond J. Gibbons, Timothy F. Christian, David O. Hodge, Todd D. Miller. Mayo Foundation; Rochester, MN, USA

**Background:** The prevalence of severely abnormal perfusion scans in patients with low risk Duke treadmill scores is low (< 10%). We sought to define a high-risk subgroup in this population using a previously published clinical score (CS), in whom perfusion imaging would most likely be abnormal.

**Methods:** We studied 1461 patients with low risk treadmill scores who had undergone exercise perfusion imaging. Follow-up was 92% complete at a mean of 7.1 ± 1 years. The CS is a simple score computed by assigning 1 point each to the following variables—diabetes, insulin use, male sex, history of MI, typical angina and each decade of age over 40. The perfusion studies were categorized by a 14-segment summed stress score (SSS) as normal (0–3), mildly abnormal (4–8) or severely abnormal (>8). Results were similar for the MI category, with the exception of angina. The CABG group had undergone exercise perfusion imaging. Following CS was < 0.0001.

**Results:** Five-year cardiac mortality for the entire population was low at 2%. The CS and the SSS were both significant (p < 0.0001) independent predictors of all 3 endpoints of cardiac death 2) cardiac death/nonfatal MI 3) cardiac death/nonfatal MI revascularization. The CS classified 21% of patients at high risk (CS > 5). The prevalence of severely abnormal scans was significantly higher in this subgroup (26% vs 9%; p < 0.001). The 5-year event-free survival for each of the endpoints based on the clinical score and the summed stress scores are shown below:

<table>
<thead>
<tr>
<th>SSS</th>
<th>Cardiac Death</th>
<th>Cardiac Death/MI</th>
<th>Late Revascularization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS ≤ 5</td>
<td>CS &gt; 5</td>
<td>CS ≤ 5</td>
<td>CS &gt; 5</td>
</tr>
<tr>
<td>0–3</td>
<td>99%</td>
<td>99%</td>
<td>97%</td>
</tr>
<tr>
<td>4–8</td>
<td>99%</td>
<td>100%</td>
<td>97%</td>
</tr>
<tr>
<td>&gt;8</td>
<td>99%</td>
<td>94%</td>
<td>96%</td>
</tr>
<tr>
<td>total</td>
<td>99%</td>
<td>94%</td>
<td>97%</td>
</tr>
</tbody>
</table>

**Conclusions:** CS and SSS are independent predictors of cardiac events. Patients with CS < 5 had low rates of death and nonfatal MI despite their perfusion findings. Patients with CS ≥ 5 have a higher rate of death/nonfatal MI (9% over 5 years) despite a low-risk treadmill score. Perfusion imaging is useful in this group for further risk stratification.

**874-3** Prognostic Implications of Hysterectomy of the ST-Segment/Heart Rate Recovery Loop Following Maximal Exercise

Christopher R. Cole, Ramf Lehtinen, Jani Vilk, Lazaro A. Diaz, JoAnne M. Foody, Peter M. Okin, Michael S. Laufer. Cleveland Clinic Foundation, Cleveland, OH; Cornell Medical Center, New York, NY, USA; Ragnar Granit Institute, Tampere University of Technology, Tampere, Finland

**Background:** The ST-segment/heart rate (ST/HR) hysteresis loop, a novel computerized diagnostic variable, improves the diagnostic accuracy of the exercise ECG but its prognostic significance has not been explored.

**Methods:** Adults undergoing symptom-limited SPECT thallium exercise testing (n = 2485, age 60 ± 10, 77% male) were followed 6.2 years. ST/HR hysteresis was defined within the loop formed by plotting ST depression against HR during exercise and the first 3 min. of recovery, divided by the change in HR during exercise. A cotangent of 0.001 mV (representative of counter-clockwise rotation) was used to define an abnormal response. Comparisons were made to the ST/HR index, a previously validated prognostic marker that adjusts the change in ST depression by heart rate change from baseline to peak exercise (abnormal ≥ 1 Hz/vheart/min) and standard ST depression. Results:

**Results:** There were 205 (8.3%) deaths. An abnormal ST/HR hysteresis and ST/HR index were present in 562 (23%) and 513 (21%) respectively. In univariate analyses, an abnormal ST/HR hysteresis was predictive of death [figure] (Relative Risk [RR] 1.47, 95% CI 1.08 - 2.01 P = 0.01). Standard ST analysis was not predictive. Adjusting for age, sex, risk factors, thallium, and the ST/HR index, ST/HR hysteresis remained predictive of outcome (adjusted RR for one standard deviation increase 1.26 95% CI 1.05 - 1.50; y² = 6, P = 0.01). The ST/HR index was not predictive in this model.
Conclusion: The ST/HR hysteresis was an independent predictor of mortality in this population even after adjusting for ST/HR index and thallium perfusion defects.

11:16 a.m.

874-4 A Simple Tool as a Strong Predictor of Mortality After Acute Myocardial Infarction in the Recanalisation Era: Predischarge Exercise Test

Caroline Bergmeier, Ralf Zahn, Rudolf Schiele, Andreas Kilkowski, Anselm K. Ott, Ulf Geserick1, Helmut Thiemis, Jochen Sienges. For the MITTRA-Investigators; 1Department of Cardiology, Herzumten Ludwigshafen, Speyer; 2Bad Dürkheim, Germany

Purpose: Is a predischarge exercise test a predictor of mortality, CABG and nonfatal reinfarction in nonselected patients (P) with acute myocardial infarction (AMI) in the recanalisation era?

Methods: The Southwest German "Maximal Individual Therapy in Acute Myocardial Infarction" (MITTRA) trial was a prospective multicenter observational study of the current treatment of AMI. 4002 consecutive P with AMI were discharged from hospital alive from 5/94 to 1/97.

Acute treatment: 56% recanalisation, 94% aspirin, 53% β-blockers, 51% ACE-inhibitors. Mean follow-up time was 18 months.

Results: 1. A workload ≤ 75 W in bicycle ergometry could be performed in 2626 P (64%). Longterm mortality was 15.6%. 2. In 466 P (10%) signs of ischemia (ST-depression ≥ 1 mm and/or angina) were observed (Longterm mortality 8.6%). 3. 1555 P (32%) achieved a workload > 75 W and signs of ischemia were absent (Longterm mortality 3.5%). 4. Results of longterm follow-up in a multivariate analysis (adjusted for age, gender, diabetes, anterior wall MI and recurrent AMI):

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>OR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>CABG</td>
<td>1.03 (1.01-1.05)</td>
<td>0.014</td>
</tr>
<tr>
<td>Readmission</td>
<td>1.05 (1.00-1.09)</td>
<td>0.026</td>
</tr>
</tbody>
</table>

Conclusion: 1. In unselected P after AMI in the recanalisation era about half of the P were not able to achieve a workload of more than 75 W in a predischarge exercise test, while about 10% showed signs of ischemia. 2. Longterm mortality in P with low exercise capacity was two times higher than in P with signs of ischemia, and five times higher than in P showing exercise capacity > 75 W and no signs of ischemia. 3. The exercise capacity is a strong independent predictor of longterm mortality in the recanalisation era, while signs of ischemia predict CABG as well as an elevated mortality, but do not predict nonfatal reinfarction.

11:30 a.m.

874-5 Which is the Best Cardiopulmonary Exercise Parameter to Identify High Risk Chronic Heart Failure Patients?

Waqar Shamim, Mohammed Yousufuddin, Marcus Fletcher, Stefan D. Anker, Andrew J.S. Coats. Royal Brompton Hospital and National Heart and Lung Institute, London, UK

Background: Peak oxygen consumption (VO2peak) is usually based on above variables. Although well established as a strong prognosticator, VO2peak still has some limitations.

Methods: A total of 298 patients aged 58 ± 12 yrs; NYHA class 2.3 ± 0.8; resting heart rate 85 ± 18; mean BP 96 ± 14; LVEF 28 ± 13; underwent symptom-limited exercise testing without imaging were followed 3.8 years. Exclusion criteria included heart failure, valvular disease, pacemaker, or uninterpretable electrocardiograms. Abnormal HRR was defined as the change in heart rate from peak exercise to 1 minute of recovery ≤12 beats. Stated response was defined as the percentage of heart rate reserve utilized (abnormal < 0.6). Abnormal ST response was defined by standard criteria.

Results: There were 157 deaths. Abnormal HRR, CRI and ST response were present in 1583 (20%), 1627 (17%) and 1194 (13%) respectively. Both abnormal HRR and CRI were present in 659 (7%). In univariate analyses, CRI, (Relative Risk (RR) 5.36 95% CI 3.92-7.32 P < 0.0001) and abnormal HRR (RR 4.16 95% CI 3.17-5.46 P < 0.0001) were predictive of mortality. All were predictors of mortality. As was ST response (RR 1.69 95% CI 1.14-2.52 P < 0.01). After adjusting for age, gender, exercise capacity, angina, baseline RBBS, cardiovascular risk factors, cardiovascular medications, prior CAD, peripheral vascular disease, and pulmonary disease, HRR (adjusted RR 1.72 95% CI 1.22-2.41 P = 0.002) and CRI (adjusted RR 1.63; 95% CI 1.32-2.35 P < 0.01) remained predictive.

Conclusion: In a low-risk population of patients referred for exercise testing, heart rate changes were powerful and independent predictors of mortality.

11:45 a.m.

874-6 Chronotropic Incompetence and Abnormal Heart Rate Recovery Predict Mortality in Patients Undergoing Exercise Testing Without Imaging

Ema O. Natalie, Christopher R. Cole, Fredric J. Pastikow, Eugene H. Blackstone, Michael S. Lauer. Cleveland Clinic Foundation, Cleveland, OH, USA

Background: Chronotropic incompetence (CRI) and heart rate recovery (HRR) have been reported to be independent predictors of mortality in moderate-risk patients undergoing exercise testing. However, little is known about this relationship in low-risk patients undergoing exercise testing without imaging. Although well established as a strong predictor, this has not been well explored in low-risk populations undergoing non-imaging exercise testing.

Methods: The Southwest German "Maximal Individual Therapy in Acute Myocardial Infarction" (MITTRA) - trial was a prospective multicenter observational study of the current treatment of AMI. 4002 consecutive P with AMI were discharged from hospital alive from 5/94 to 1/97.

Methods: A total of 298 patients aged 58 ± 12 yrs; NYHA class 2.3 ± 0.8; resting heart rate 85 ± 18; mean BP 96 ± 14; LVEF 28 ± 13; underwent symptom-limited exercise testing without imaging were followed 3.8 years. Exclusion criteria included heart failure, valvular disease, pacemaker, or uninterpretable electrocardiograms. Abnormal HRR was defined as the change in heart rate from peak exercise to 1 minute of recovery ≤12 beats. Stated response was defined as the percentage of heart rate reserve utilized (abnormal < 0.6). Abnormal ST response was defined by standard criteria.

Results: There were 157 deaths. Abnormal HRR, CRI and ST response were present in 1583 (20%), 1627 (17%) and 1194 (13%) respectively. Both abnormal HRR and CRI were present in 659 (7%). In univariate analyses, CRI, (Relative Risk (RR) 5.36 95% CI 3.92-7.32 P < 0.0001) and abnormal HRR (RR 4.16 95% CI 3.17-5.46 P < 0.0001) were predictive of mortality. As was ST response (RR 1.69 95% CI 1.14-2.52 P < 0.01). After adjusting for age, gender, exercise capacity, angina, baseline RBBS, cardiovascular risk factors, cardiovascular medications, prior CAD, peripheral vascular disease, and pulmonary disease, HRR (adjusted RR 1.72 95% CI 1.22-2.41 P = 0.002) and CRI (adjusted RR 1.63; 95% CI 1.32-2.35 P < 0.01) remained predictive.

Conclusion: In a low-risk population of patients referred for exercise testing, heart rate changes were powerful and independent predictors of mortality.

POSTER

1161 Signal Transduction in Growth Regulation

Tuesday, March 14, 2000, Noon-2:00 p.m.
Anaheim Convention Center, Hall A
Presentation Hour: 1:00 p.m.-2:00 p.m.

1161-142 Stretch Stimulates Phospholipase C Activity and Increases Intracellular Calcium Ion Levels in Neonatal Rat Ventricular Myocytes


Background: Stretch plays a key role in development of hemodynamic over-
load-induced left ventricular hypertrophy. The signal transduction pathways involved in transmembrane of the stretch signal to the nucleus are largely unknown. We investigated whether phospholipases C (PLC) and D (PLD) and intracellular calcium (Ca²⁺) are part of the signal transduction pathways of stretch induced hypertrophy of cardiomyocytes.

Methods: Cardiomyocytes were isolated from the ventricles of neonatal rats and grown on flexible membranes. Cyclic stretch (20%, 1 Hz) was subjected to the cells by applying intermittently vacuum below the membranes. Intracellular calcium was measured fluorimetrically using Fura2-AM. PLC activity was determined by formation of inositol-trisphosphate (IP₃) after loading with 10 μM thapsigargin. Ca²⁺ elevation upon stretch was attenuated to increases of 47% and 42% over control, respectively (p < 0.05). Furthermore, there was a positive correlation between [Ca²⁺]r elevation and amplitude of stretch (r = 0.98, p < 0.01).

Results: UV immediately inhibits RNA synthesis in a dose dependent manner, reducing RNA synthesis to 40% of fibroblasts and to 60% in myocytes was found 24 h later. The frequency of transcribed strand of the inactive gene was found in fibroblasts. CPD removal specific enzyme T4 endonuclease V and quantitative Southern blot analysis. The data also suggest that chronic angiotensin converting enzyme inhibition not only ameliorates cardiac remodeling, but potentially restores the normal responsiveness of homologous-related signaling such as: JNK/p38 pathways: "p = 0.01 vs. the control, **p < 0.05 vs. vehicle.

Conclusion: The Ang-induced activation of multiple MAPKs is differentially involved in the control of CHF. The altered activation of JNK/p38, but not of ERK, may be involved in cellular events underlying the CHF transition. The regulatory control of mesodermal differentiation into myocyte lineages (smooth, skeletal and cardiac) is apparently controlled at the highest levels of development and progressively increases throughout cardiogenesis. Moreover, tissue-specific expression of cell cycle regulatory proteins, unlike hematopoietic and endoderm derived organ systems, is present and may contribute to cell cycle withdrawal via protein down-regulation and compartmentalization.

Analysis of Repair of UV-Induced DNA Damage in Transcriptionally Active and Inactive Genes in Rat Cardiac Fibroblasts and Terminally Differentiated Myocytes

Caroline G.C. van der Wees, Maaike P.G. Vreeswijk, Marion Persoon, Leon H.F. Mullenders, Arndou van der Laarse. Leiden University Medical Centre, Leiden, The Netherlands

Background: Nucleotide excision repair (NER) is a major repair pathway responsible for the removal of a variety of structurally unrelated DNA lesions. Within NER two subpathways can be distinguished: transcription-coupled repair (TCR) and general repair (GR). The repair of UV-induced cyclobutane pyrimidine dimers (CPD) in transcriptionally inactive genes is largely unknown. To determine whether transcriptionally differentiated cardiomyocytes are able to repair DNA damage by NER, we studied induction and repair of UV-induced cyclobutane pyrimidine dimers (CPD) in transcriptionally inactive genes.

Methods: Myocytes and fibroblasts were isolated from ventricles of neonatal rats. To determine the level of RNA synthesis [³H]-thymidine prelabelled cells were incubated in the presence of sH-uridine after UV irradiation. The incorporation of [³H]-uridine into cardiomyocytes during mouse cardiogenesis. By day 12.5, nearly 18% of cardiomyocytes were unlabeled with PCNA, cdk2 or BrdU. This reached nearly 40% at day 15 and less than 1% at day neonatal day 3. Cyclin D family member expression was both temporally and spatially regulated. Cyclin D1 protein was present in the nucleus of proliferating cells from embryonic day 9.5 p.c. Expression progressively decreased by the end of the neonatal period. Cyclin D2 expression appeared at day 11.5 p.c. and was detected in the whole heart, but not in the myocardium. Cyclin D3, first detected at embryonic day 12.5 p.c. within the nucleus, remained present throughout cardiogenesis. Cyclin D4 expression was first detected at embryonic day 9.5 p.c. and continued to be expressed throughout the neonatal period.

Conclusions: These data demonstrated cell cycle arrest in subsets of cardiomyocytes beginning during the mid-embryonic period of cardiac development and progressively increases throughout cardiogenesis. Moreover, tissue-specific expression of cell cycle regulatory proteins, unlike hematopoietic and endoderm derived organ systems, is present and may contribute to cell cycle withdrawal via protein down-regulation and compartmentalization.

1161-I Abstracts – Cardiac Function and Heart Failure

1161-143 Transcription Factor Control of Myogenic Differentiation in a Myogenic Model Cell Line

Merry Davidson, Jennifer Cho, Xiaojun Qu, Donald Chen, Hal A. Skripochnik. College of Physicians and Surgeons at Columbia University, New York, New York, USA

The regulatory control of myogenic differentiation into myocyte lineage (smooth, skeletal and cardiac) is apparently controlled at the highest levels of development and progressively increases throughout cardiogenesis. Moreover, tissue-specific expression of cell cycle regulatory proteins, unlike hematopoietic and endoderm derived organ systems, is present and may contribute to cell cycle withdrawal via protein down-regulation and compartmentalization.
line derived entirely from adult human cardiomyocytes. Cells do not sponta-
necessarily contract in culture, but are capable of terminally differentiating when
plated in low serum conditions, similar to H9c2 cells. To further understand the
regulation of transcription factors involved in determining their cellular phenoe-
types, we analyzed mRNA expression patterns for presence and absence of
in a number of known regulators or markers of both skeletal and cardiac muscle lineages.
Reverse transcription followed by PCR with specific primers indicated
of GATA-4 and ANP (unpublished), but not GATA-4 NKX2.5 mRNA was
expressed only in differentiated cells, consistent with the expression of car-
diac-specific lineage markers. Transient transfection overexpression of TGF-β
family members and proliferating cell lines resulted in the transient repression of
expression of NKX2.5, indicating competence for cardiomyocyte determination.
Interestingly, Myf5, but not MyoD or myogenin, was detected at both the pro-
line and mRNA level in proliferating and differentiating cells. No downstream
markers of the skeletal muscle lineage were expressed, indicating a block in the
skeletal muscle paradigm.

Conclusion: These data suggest the presence of permissive periods for
cardiomyocyte determination and the ability of cardiomyocyte-derived muscle
cell lines to inhibit skeletal muscle determination despite Myf5 expression.

1161-147 Sp1-Dependent Expression of the Cardiac
Tropinin T (cTNT) Gene in Avian Embryonic
Myocytes can be Compensated for by the MEF-2
Site of the cTNT ‘Cardiac Element’

Anthony Azarbe, Doft S, McElhinney, S. B. Lankin, Ian K. Farmace, Charles
P. Ordahl. California, San Francisco, CA, USA.

Background: Sarcomeric proteins are coordinately expressed during my-
cardial differentiation, implying common mechanisms of cardiac-specific
gene regulation, cTNT is expressed throughout development in avian cardiac
myocytes (CM) and until day 19 of embryogenesis in skeletal muscle (SM).
A minimal promoter (~129 cTNT) is sufficient for high levels of expression
in embryonic CM. High levels of expression in CM, however, require an addi-
tional promoter element between -268 and -201, which has been termed the
‘cardiac element’ (CE). In addition to binding sites for other transacting
factors, the CE contains a GC box. cTNT expression was restored to levels greater than those
seen with CM upstream of wild-type minimal promoter.

Results: cTNT expression was restored to levels greater than those
seen with CM upstream of wild-type minimal promoter, cTNT expression was restored to levels greater than those
seen with CM upstream of wild-type minimal promoter.

Conclusion: These result suggest that the Sp1 binding site is important for
operation of the minimal promoter in embryonic CM, but can be compen-
sated for by upstream placement of the A/l-rich site from the cTNT CE.

1161-148 Novel Induction of Heat Shock Proteins by
Magnetic Field Stress in Myocytes in vitro and in vivo

Masateru Nakao, Richard Wu, Martin Blank, Arthur Pilla, Reba Goodman,
Hal A. Skopicki. Osaka Medical College, Osaka, Japan; The College of
Pennsylvania, Philadelphia, Pennsylvania; Children’s Hospital, Philadelphia,
Pennsylvania; MCP Hahnemann, Philadelphia, Pennsylvania, Cowance,
Princeton, New Jersey, USA

Background: We and others found that baseline intracellular Na+ is approx-
imately two times higher in diabetic (DM) cardiomyocytes than in Control
(CON). We also find that Na+ (0.1–10 mM) can depress State 3 respiration
in isolated heart mitochondria. The increase of apoptotic markers in close
proximity to the ischemic area has been the focus of investigation.

Methods: To further evaluate this hypothesis Myo I were isolated from
hearts of C57/BL6 mice and streptozotocin-induced (STZ) diabetic (DM) rats. Mitochondria were
resuspended and respiring complex I activity was assayed.

Results: In DM, Na+ decreased State 3 to lower levels than in CON. Gas+
(0.035 PM) reversed the Na+ depressant effect on State 3 in CON (p < 0.05),
above baseline in both CON and DM. Similar Na+ and Ca2+ induced changes
were found for the rate of ADP phosphorylation, but not for State 4 respiration
and ADP/O ratio.

Conclusion: These data support our hypothesis that increased intracellular Na+ in DM can lead to depletion of Mito Ca2+ which in turn
influence of ATP synthesis.
Low Incidence of Ventricular Arrhythmias in Patients on Low Dose Parenteral Inotropes at Home
Waiting Cardiac Transplant Using an External Wearable Defibrillator

Simon Maybaum, Marie Ellena Cordisco, Donna Mancini. Columbia University, New York, New York, USA

Methods: 18 patients listed for transplant were discharged home with a LIFECOR external defibrillator (11 patients on inotropes, 7 without inotropes). 9 patients were treated with amiodarone and 8 with a beta-blocker. The LIFECOR defibrillator is a vest-like garment that uses 4 sensing chest electrodes. The investigator programs the minimum heart rate for arrhythmia detection and defibrillation energy level for each patient. This device provides continuous EKG monitoring and can discharge 2 shocks at 200 or 300 joules. Arrhythmia detection rate was programmed above 140 bpm (range 140-170 bpm). 2 lead EKG strips generated by device alarms or patient symptoms were reviewed. An event was defined as 3 or more consecutive ventricular beats.

Results: A total of 10,183 monitored hours (mean wear time per patient 566 ± 955 hours) were reviewed. There were only 3 (asymptomatic) events. 2 of the 3 events were in the inotrope group. One patient off inotrope was hospitalized with a wide complex tachycardia that was determined to be rapid atrial fibrillation with aberrancy. There was 1 sudden death in a patient on inotrope who was not wearing his defibrillator at the time. In 004 hours of previous monitoring, he had had no events.

Conclusions: Although we continue to recommend continuous monitoring for patients on parenteral inotropic therapy at home or in hospital, there appears to be a low incidence of complex ventricular arrhythmias in patients with and without CHF on low dose parenteral inotropic therapy.

Angiotensin II-Type 1 (AT1) Receptor Blockade
With 80 mg of Valsartan in Patients With Congestive Heart Failure (CHF)

Ulrich P. Jorde, Vana Suryavadekar, Thierry H. Le Jeunet. 1Columbia University; Albert Einstein College of Medicine, New York, New York, USA

Background: AT1-receptor blockers (ARB) may provide an alternative or additional means to angiotensin converting enzyme inhibitors (ACEI) to supress the renin-angiotensin system in CHF. We have previously reported variable vascular reactivity (VR) to angiotensin II (AngII) in pts with CHF, i.e. the peak response (PR) in systemic blood pressure (SBP) to 5 rig/kg (AngII) ranged from 0-27 mmHg. It is unknown whether this variability in VR is relevant in the response to standard dose ARB.

Methods: 82 pts with CHF (NYHA III/IV [28/31], LVEF < 40% [22/0]), serum creatinine < 2.5 mg/dl who had received full dose (40 mg/day of a long acting or 150 mg of a shortacting) ACEI for at least 3 months were studied. Ascending (2.5, 5, 10, 20, 40, 60, 80, 100, 150 mg) doses of enoximone Ag (Enaflit Ag, Novartis, Basel, Switzerland) were injected prior and 90 min after oral administration of 80 mg of valsartan to determine the dose required to abolish a rise in peak SBP of 20 mmHg (p<0.05). SBP and heart rate were recorded continuously using beat-to-beat monitoring (Colin Corp, San Antonio, Texas).

Results: The PD 20 before and after valsartan is shown in the figure. Mean PD20 changed from 10.5 ± 4.9 to 7.6 ± 2.4 (±2.5A) mHg. The PD 20 was fully inhibited (i.e. PD20 > 75 mHg) in 24/34 pts. When pts were grouped according to the initial PD20 (0-6, 6-10, >10), the PR was fully inhibited in 2/11, 10/11, and 11/11 pts, respectively. PD20 before and after ARB were correlated significantly (R = 0.55, P = 0.001).

Conclusion: 00 mg of valsartan scoloty is not sufficient to fully inhibit the PR to All, i.e. block all AT-1 receptors. In about 1/3 of pts with CHF on full dose ACEI therapy, the dose of ARB required for full blockade is variable in these pts and may be defined by the pressure responses to All.

Arun J.C. Prahash1, Sudhir Gupta, Inder S. Anand. 1Department of Medicine; Division of Cardiology; VAMC and University of Minnesota, Minneapolis, USA

Background: ACE-inhibition (ACEI) has been proven to improve ventricular remodeling and survival following myocardial infarction (MI). We compared the effects of ACEI (Enalapril 1 mg/kg), Angiotensin II receptor blocker (ARB; Candesartan 10 mg/kg) and their combination on ventricular hypertrophy and remodeling in a rat model of 6 weeks post-MI in all hearts. At 6 weeks, hemodynamics was studied in separate groups by carotid catheterization (Group 1: Mean arterial and LV end-diastolic pressure) and isolated heart perfusion (Group 2: isovolumic LV developed pressure and dP/dt). Ventricular septal thickness was quantified in fixed tissue sections to measure compensatory hypertrophy.

Results: ACE-I and ARB either alone or in combination with ACEI significantly reduced compensatory LV hypertrophy following MI while ACEI alone did not. Both ACEI and ARB reduced LV chamber remodeling with the combination providing added benefit to either of the treatments alone. While all treatments reduced invivo LVDP, ARB treated rats had significantly lower MAP. ACEI and ARB normalization were implemented in a LV systolic function in isolated hearts.

Conclusion: Post-MI ARB favorably alters LV chamber remodeling and cardiac hypertrophy and provides additional benefit when combined with ACEI.
Background: Several randomized controlled trials have demonstrated the efficacy and safety of beta-blockers in chronic heart failure (CHF) in reducing mortality and hospitalization. However, there is a lack of consensus regarding the optimal beta-blocker dose for patients with CHF, and few data on dose-related effects. This study aimed to assess the dose-responsiveness of carvedilol, a beta-blocker prescribed for CHF, in patients from different clinical settings.

Methods: We reviewed 194 cases of chronic carvedilol use in clinical practice. Baseline predictors of tolerability were analyzed with uni- and multivariate analyses. Factors that indicated worse tolerability were age (relative risk (RR) 1.02, 95% confidence interval (CI) 1.01-1.03), low diastolic blood pressure (RR 1.03, 95% CI 1.01-1.05) and raised LV end-systolic pressure (RR 1.02, 95% CI 1.00-1.05). However, no single baseline parameter was an independent marker of inability to tolerate carvedilol.

Results: For the entire group, LVEF significantly increased by 6.03 ± 0.70% (p < 0.001). The increase in LVEF was greater in IDC compared to ISC (76 pts) and diabetes (86% (117 pts), peripheral vascular disease (85% (51 pts), and baseline LVEF 31 ± 6%). Carvedilol dose was determined by patient tolerance and did not differ by site of practice. Doses ranged from 6.25 mg/day to 100 mg/day. LVEF was re-evaluated 4-8 months following maintenance therapy. The change in LVEF was 2.23 ± 0.06%, 7.56 ± 1.07%, and 8.09 ± 1.58%, respectively (p < 0.001).

Conclusions: The dose-responsiveness of carvedilol in CHF is significant and consistent across different clinical settings. Further studies are needed to determine whether the observed benefits can be maintained with chronic therapy.
**Poster 1163**

**Predictors of Prognosis and Outcomes in Elderly Patients**

Tuesday, March 14, 2000, Noon–2:00 p.m.
Anaheim Convention Center, Hall A
Presentation Hour: 1:00 p.m.–2:00 p.m.

**Background:** Death rates from heart disease have declined in the United States since the 1950’s. The purpose of our study was to determine whether this benefit occurred in all subgroups of the population by age, gender, and race over the last decade in Los Angeles County.

**Methods:** We studied 4,993 patients age ≥75 undergoing CABG or PTCA. CABG may confer a survival advantage compared with PCI in patients ≥75 years of age. This difference is likely to reflect the lesser severity of heart disease in patients assigned to CABG, and superior surgical results in elderly patients compared with younger patients.

**Results:** Crude death rates for heart disease fell for patients over the age of 65 between 1987 and 1997 from 299 per 100,000 population per year to 171 per 100,000 patients (p = 0.001). Among patients aged ≥75 years in the ERV group, 2/4 (50%) had an EF < 25%, compared to 16/44 (36%) of the younger IMS patients (p = 0.009). When age was examined as a continuous variable, a significant inverse association with survival was found (p = 0.009). The estimated adjusted probability of survival was 90.1% at 1 year and 78.4% at 4 years. CABG patients had a 25% reduced hazard of mortality versus PCI patients (RH 0.75, 95% CI 0.64–0.89).

**Conclusion:** The majority of elderly patients survive 4 or more years after CABG or PTCA. CABG may confer a survival advantage compared with PTCA.
differences in MR grade or IMLC detected between young or old patients irrespective of treatment strategy.

Conclusions: These data suggest that elderly patients in the ERV group had a significant excess of low ejection fractions and severe MR zone-H2 at randomization. This excess of high-risk findings among elderly patients in the ERV may partly explain the apparent lack of benefit from an ERV strategy for patients ≥75 years of age in the SHOCK trial.

1163-123
Serial Echocardiographic and Clinical Follow-up in Medicare-Aged Patients Undergoing Percutaneous Balloon Mitral Commissurotomography

Richard A. Krauslik, John J. Warner, Andrew Wang, Katherine Kiskel, J. Kevin Harrison, Thomas M. Bashore. Duke University Medical Center, Durham, NC, USA

Background: Percutaneous posterior mitral commissurotomy (p-PBMC) can be performed safely in patients (pts.) of Medicare age. The long-term echocardiographic and clinical results in this age group remain unclear.

Methods: Serial 2-D and Doppler echocardiographic measures along with clinical findings were assessed in 57 elderly pts (ages 65-85, mean = 71) compared to 285 younger pts (ages 12-64, mean = 47) undergoing lnoue PBMC.

Results: Baseline, 24 hour, 6 month and 3 year data were analyzed. Baseline echocardiographic scores were significantly higher in the Elderly (9.8 vs. 8.5, p = 0.001). In elderly pts, the post-procedural mitral gradient by echocardiography was similar (5.9 vs. 6.1 mmHg, p = NS), the planimetered MVA was smaller (1.7 vs. 2.0 cm², p = 0.006) and there was no difference in mitral regurgitation (MR) compared with the younger group. At 6 months the gradient was 5.6 vs. 5.4 mmHg (p = NS), the planimetered MVA was 1.6 vs. 1.8 cm² (p = 0.003) and the MR grade was 1.5 vs. 1.3 (p = NS). By 3 years the gradient was 6.5 vs. 5.4 mmHg (p = NS) and MVA 1.4 vs. 1.8 (p = 0.002). MR grade was 1.8 compared with 1.3 in the younger pts (p = NS). The mean change in the MVA from baseline was similar in both groups. From a symptomatic standpoint, there was no evidence of worsening in the elderly population over the same follow-up period. Three year event-free survival (death, repeat PBMC or mitral valve replacement) was similar in both groups (91% in young and 80% in the elderly group).

Conclusions: Compared to a younger aged group the initial result of percutaneous balloon mitral commissurotomography in the Medicare aged population is less effective. Over time, serial echocardiographic data reveal a similar decline in the MVA in both groups. Symptoms remain improved, though, and long term outcome appears identical between the two groups.

1163-124
Predictive Value of the Annual Electrocardiogram (ECG)

Mahesh Amin, Bruce J. Faireau, James L. Fozard, Daphne S. Gage, Jennifer R. Copeland, Bernadette O. Stevenson, William E. Hees, Kevin J. Ferrick. Morton Plant Mouse Health Care and Montefiore Medical Center, Bronx, New York, USA

Background: ECGs are often performed routinely during annual physical examinations without clear benefit in risk stratification. The predictive value of performing these ECGs in unknown.

Methods: In the Florida Geriatric Research Program (FGRP), longitudinal medical information was collected annually from men and women volunteers 65 years and older. Over 1700 volunteers per year have participated for the past 25 years. The data include health history obtained using self reported answers to a questionnaire in addition to a yearly ECG, screening blood work and blood pressure measurement. Mortality data is gathered through death certificates and verified by the primary care physician's medical records. ECGs from 1992 to 1999 were interpreted by a board certified cardiologist blinded to clinical status. ECGs for the 5 years preceding cardiovascular events or permanent pacemaker implantation were reviewed for 28 pre-determined abnormalities.

Results: Of the 3153 charts reviewed, hyper-tension was found in 43% of the patients, 24% had established heart disease. ECG conduction abnormalities were noted in 29% (left anterior hemiblock 12%, first degree atrioventricular (AV) block 7%, right bundle branch block 6%, left bundle branch block 3.1%, second degree AV block 0.5%, left posterior hemiblock 0.2%), left ventricular hypertrophy in 12% and atrial fibrillation in 12%. Between 1992 and 1999, 322 myocardial infarctions, 565 new complaints of angina, 268 coronary artery bypass grafts and 38 percutaneous transluminal coronary angioplasty procedures occurred. No single abnormality identified on the ECG within 5 years of hospitalization for patients ≥75 years of age in the SHOCK trial.

Conclusions: The routine annual ECG is not predictive of an adverse cardiac event in an elderly patient without signs or symptoms of unstable cardiac disease.

1163-125
Chronic Heart Failure in the Elderly: The Value of Cardiopulmonary Exercise Testing in Risk Stratification

L. Cieri Davies, Darrell P. Francis, Massimo Piepoli, Adam C. Scott, Piotr Polkowski, Andrew J.S. Coats. National Heart & Lung Institute, Royal Brompton Hospital, Dovehouse St. London, SW3 6LY, UK

Background: Chronic heart failure (CHF) is common in the elderly and is associated with a poor prognosis. Cardiopulmonary exercise testing is widely used in the assessment of younger patients with CHF, but its usefulness in older patients is unclear. We set out to assess prognostic markers in a cohort of CHF patients over the age of 70 with 2-year follow-up.

Methods: Between January 1992 and May 1997, 50 patients with CHF over the age of 70 (mean age 75±4 years [SD 4.3, range 70±4-81±6]) female) were evaluated at the Royal Brompton Hospital. They underwent cardiopulmonary exercise testing (peak oxygen consumption (peak VO2): mean 1.2±0.2 ml/kg/min [SD 4.7], VE/VO2 slope: mean 39±7, SD 11±6), assessment of functional status (New York Heart Association [NYHA] class: 3 class I, 25 class II, 20 class III, 2 class IV), radionuclide measurement of left-ventricular ejection fraction (mean 32.8% [SD 14.3]), measurement of serum sodium (mean 138 mmol/l [SD 2.8]) and echocardiography (end-diastolic dimension: mean 6.1 cm [SD 1.1]; end-systolic dimension: mean 4.7 cm [SD 1.5]).

Results: At the end of the follow-up period in May 1999, 25 patients (52%) died (median time to death 23.9 months, interquartile range 9.2–15.8 months). The median follow-up duration for the survivors was 47.7 months (interquartile range 31.5–53.5 months). On univariate analysis, VE/VO2 slope (p = 0.001), NYHA class (p = 0.011), peak VO2 (p < 0.001) and serum sodium (p = 0.001) had significant predictive power. A multivariate model using these five variables identified only VE/VO2 (p = 0.01), NYHA class (p = 0.05) and peak VO2 (p < 0.001) as conveying significant independent prognostic information.

Conclusions: Elderly patients with CHF have a high mortality (52% at 2 years). Cardiopulmonary exercise testing provides important information for risk stratification within this group and a role in their assessment.

1163-126
Is Treadmill Exercise Testing Useful in the Elderly? A Population-Based Study in Olmsted County, MN

Tauciy Y. Goraya, Steven J. Jacobsen, Susan A. Weston, Todd D. Miller, Patricia A. Pellicci, Bernard J. Gersh, Veronica L. Roger, Mayo Clinic, Rochester, USA

Background: The prognostic value of TMET has been derived primarily in referral populations of middle-aged patients (median age < 65 years) at tertiary-care centers. The generalizability to community dwelling elderly persons is uncertain.

Methods: A population-based study of persons living in Olmsted County, MN who underwent TMET (1987–1990) was undertaken to test the hypothesis that TMET has equal prognostic value among elderly (~65 years, n = 514) and younger (~ <35 years, n = 2953) persons and to examine its incremental value over clinical data.

Results: Elderly patients were more likely to have a history of MI, diabetes, hypertension, hyperlipidemia and comorbidity (all P < 0.05). Younger patients achieved a higher workload (10.7 vs 8.0 METS, P < 0.001) and had fewer positive exercise ECG responses (0.1% vs 27.0%, P < 0.001). At 6 years, overall survival (63% vs 92%, P < 0.05) and event-free (cardiac death, nonfatal MI and heart failure) survival (66% vs 95%, P = 0.05) were worse in the elderly. The univariate associations between TMET variables and outcome are shown below:

<table>
<thead>
<tr>
<th>TMET Variable</th>
<th>All-Cause Mortality</th>
<th>Cardiac Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young</td>
<td>Elderly</td>
<td>Young</td>
</tr>
<tr>
<td>Workload</td>
<td>0.74‡</td>
<td>0.75‡</td>
</tr>
<tr>
<td>(0.69, 0.79)</td>
<td>(0.70, 0.81)</td>
<td>(0.71, 0.80)</td>
</tr>
<tr>
<td>Angina</td>
<td>1.48</td>
<td>1.12</td>
</tr>
<tr>
<td>(0.65, 3.40)</td>
<td>(0.59, 1.89)</td>
<td>(1.85, 5.59)</td>
</tr>
<tr>
<td>Positive</td>
<td>1.73</td>
<td>1.05</td>
</tr>
<tr>
<td>(0.92, 3.28)</td>
<td>(0.89, 1.00)</td>
<td>(1.89, 4.66)</td>
</tr>
</tbody>
</table>

Risk Ratios (95% confidence intervals): †P < 0.001; ‡P < 0.05

After adjustment for clinical variables, workload was the only additional TMET variable predictive of death and cardiac events (all P < 0.0001) and the strength of association (16% reduction in mortality for 1 MET increase in exercise capacity) was similar in both age groups. Each MET increase in exercise capacity also resulted in 10% and 16% reduction in cardiac events for younger and older patients respectively.

Conclusions: In this population-based study of elderly residents, TMET provides incremental prognostic information to clinical data; all TMET vari-
ables, workload exhibits the strongest association with outcome and its pro-
tective effect is of the same magnitude as in the younger persons.

**882**
Cardiac Transplant: Rejection and Immunosuppression

Tuesday, March 14, 2000, 2:00 p.m.–3:30 p.m.
Anaheim Convention Center, Room 304A

**882-1**
Cellular Rejection and Rate of Progression of Transplant Vasculopathy: A 3 Year Serial Intravascular Ultrasound Study

Javier Jimenez, Sams R. Kapadia, Mohamad H. Yamani, Luba Platt, Randall E. Starring, James e. Young, Steven L. Issen, K. Murat Uzcu. The Cleveland Clinic Foundation, Cleveland, OH, USA

**Background:** Although intravascular ultrasound is established as the optimal method for early detection of transplant vasculopathy, the risk factors deter-
mind the rate of progression remain uncertain.

**Methods:** We evaluated 47 patients undergoing heart transplantation from 1990 to 1995. Intravascular ultrasound was performed at baseline (within 2 months) and annually for three years to determine maximum intimal thickness and area stenosis in each coronary segment. Vasculopathy was defined as a lesion with intimal thickness > 0.5 mm not present at baseline. Biopsies were scored by assigning a numerical weight to each ISHLT grade during the first year.

**Results:** New lesions were identified in 30 patients. Average biopsy score was > 1.0 in 35 patients with a significant linear correlation between the rate of intimal thickening and biopsy score ($r = 0.47$, $p = 0.004$). However, lesions were detected in 7 of 12 (58%) patients with biopsy score < 1.0. Comparing biopsy scores > 1.0 vs. < 1.0, the rate of progression of intimal thickening was similar ($97 = 96$ vs. $97 = 110$ micrometers/year, $p = 0.88$).

**Conclusions:** The rate of progression of vasculopathy correlates with biopsy score. However, lower biopsy scores do not preclude progressive vasculopathy. These findings suggest that injury from cellular rejection con-
tributes to vasculopathy but does not explain disease severity in all patients.

**882-2**
Expression of Suppressors of Cytokine Signalling (SOCS) in Experimental Cardiac Transplant Rejection

Pauline Diamond, Ann McGrath, Oiuingshian Jian, Ramshon Murphy, Catherine Godson, Declan Sugrue, Hugh McCann, Hugh R. Brady. Centre for Molecular Inflammation and Vascular Research, Department of Medicine and Therapeutics, University College Dublin, UK. *Division of Transplant Nephrology, Mount Sinai Medical Center, 1 Gustave Levy Place, New York, USA

**Background:** The suppressors of cytokine signalling proteins function as negative regulators of cytokine-activated Jak/STAT signal transduction. The present study assessed the profile of SOCS in a rat heterotopic model of acute cardiac transplant rejection.

**Methods:** Animals were sacrificed at days 1, 3, 5 and 7 post-transplan-
tation and the native and donor heart retrieved. Expression of SOCS-1, SOCS-3 and leukocyte trafficking determinants was assessed by RT-PCR.

**Results:** Constitutive expression of SOCS-2 and cytokine inducible SH2 domain (CIS)-1 was detected in all tissues; CIS-1 mRNA levels were ele-

timated by RT-PCR and leukocyte trafficking determinants was assessed by RT-PCR. Results: Constitutive expression of SOCS-2 and cytokine inducible SH2 sequence (CIS)-1 was detected in all tissues; CIS-1 mRNA levels were ele-

**Inferences:** 1) TI, a sensitive marker of early diastolic and systolic perfor-


**882-3**
Can Combined Indices of Diastolic and Systolic Myocardial Performance Reliably Predict Cardiac Allograft Rejection?

Krishnamoorthy Vivekanandan, Thomosan Kalapura, Myung H. Park, Robert Scott, Richard V. Milani, Mandep P. Mebra. Ohtsner Heart and Vascular Institute, New Orleans, Louisiana, USA

**Background:** Systolic and diastolic myocardial performance characteristics are altered during allograft rejection. Non-invasive diagnostic markers of allo-

graft rejection have thus far not been found to be clinically useful.

**Hypothesis:** We examined the clinical utility of the Tei Index (TI), a com-

**Method:** Twenty heart transplant recipients with moderate cellular rejec-
tion (ISHLT Grade > 3A) underwent echocardiographic assessment to derive the TI at baseline (rejection free), during treatment for rejection, and following recovery from rejection (Group I). A parallel group of 20 non-rejectors (ISHLT Grade ≤ 1A) were also similarly examined to serve as controls (Group II).

**Results:** In Group I patients, there was a mean increase of TI by 97.8% ($p < 0.0001$) during the rejection episode as compared to baseline. Following treatment, TI dropped to its baseline value. In the control group there was no significant change in TI over time. The change in TI in patients with >IIIA cellular rejection was independent of the rejection fraction ($EF$) at baseline and change in $EF$ during the rejection episodes.

![Graph showing relationship between TI and baseline vs. rejection]

<table>
<thead>
<tr>
<th>Group I (n = 20)</th>
<th>Baseline</th>
<th>Rejection</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>TI</td>
<td>0.42 ± 0.12</td>
<td>0.42 ± 0.12</td>
<td>0.42 ± 0.11 NS</td>
</tr>
<tr>
<td>p-value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Inferences:** 1) TI, a sensitive marker of early diastolic and systolic perfor-

**882-4**
Increased Incidence of Atrial Flutter Associated With the Rejection of Heart Transplantation

Guanggen Cui, Jon Kobashigawa, Luyi Sen. UCLA Medical Center and UCLA School of Medicine, Los Angeles, CA, USA

Atrial fibrillation (AF) and flutter (AF) are common dysrhythmias following heart transplantation (HXT), however, their etiology and clinical significance have been not been defined. To determine the precise incidence of persistent AF and AF, and their association with the rejection of HXT, 968 consecutive patients undergoing orthotopic HXT at UCLA Medical Center between February 1984 to December 1990 were included in the study. Total of 30 patients had AF with total of 92 episodes, 11 of them converted to AF. Seventy-eight patients had AF with total of 80 episodes, 7 of them converted to AF. The incidence of AF (9.3%) was same as AF (8.7%). Significant inter-atrial conduction defect
manifested by increased basal activity of the Rikenase and Phospholipase C in the presence of A23187 and the presence of anti-inflammatory cytokines such as IL-4 and IL-10. This increased basal activity was associated with an increased production of the inflammatory cytokines IL-12 and TNF-α.

Conclusions: The results suggest that the increase in basal activity of the Rikenase and Phospholipase C in the presence of A23187 and the presence of anti-inflammatory cytokines such as IL-4 and IL-10 may be contributing to the increased production of the inflammatory cytokines IL-12 and TNF-α, which may be contributing to the increased basal activity of the Rikenase and Phospholipase C in the presence of A23187 and the presence of anti-inflammatory cytokines such as IL-4 and IL-10.

**References:**
chronic heart failure (CHF) patients is less oxidative than in controls (C), leading to a reduced max O2 uptake (mV02). Whether this result from a decreased substrates delivery or from an impaired mitochondrial oxidative capacity remains unclear. Although the MI density and enzyme content may be diminished in CHF, the MI respiratory features have never been directly assessed in CHF.

Methods: We obtained SM vastus lateralis biopsies in 12 CHF patients at the time of transplantation, in 8 sedentary C (SED) and in 9 physically active C (PA). All the CHF and C had their mV02 (ml/min/kg) measured. After saponin permeabilization and with saturated levels of O2 and substrates, we measured the SM tissue O2 uptake (umol/min/kg dry weight) in an oxygraphic chamber without phosphate acceptor (Vo2), and with increasing levels of the acceptor ADP that allowed to measure the max tissue O2 uptake (Vmax), the Km for ADP (µM) and the acceptor control ratio (ACR = Vmax/Vo2).

Results: As the saponin permeabilization keeps the whole MI population within the cell architecture, the Vmax defines the subject's MI oxidative capacity, the Km (CHF:148 ± 36, SED:111 ± 23, PA:55 ± 10) represents the MI affinity for ADP and the ACR (CHF:3.1 ± 0.5, SED:2.9 ± 0.6, PA:6.5 ± 1.1) defines the phosphorylation-Vo2 coupling efficiency. The Vo2, Vmax and mVo2 are shown on figures. Values: means ± SEM, *p < 0.05 vs CHF.

Conclusion: In CHF patients, the intrinsic SM MI oxidative capacity, MI affinity for ADP and coupling efficiency just reveal untraining, being all similar to the one of SED. This opens the question whether an impaired substrate delivery would represent the main determinant of the abnormal MI exercise metabolism in CHF.

Alveolar-Capillary Diffusion Impairment and Lung Water (LW) Content in Severe Heart Failure (HF)

Gianfranco Marini, Francesco Azzolina, Marco Ghisletti, Marco Gresi, Maurizio Bussotti, Maurizio Guazzi. Institute of Cardiology, University of Milan, Centro Cardioologico "Monzino", IRCCS, Milan, Italy

Background: The relationship between LW content increase and alveolar-capillary diffusion for carbon monoxide (DLco) reduction in severe HF has not been completely defined.

Methods: LW, lung volumes and DLco were evaluated in 15 normal subjects and in 28 patients with severe HF (NYHA III-IV), in the latter before and 4 days after fluid removal by diuretic administration. We calculated the DLco (ml/min/mmHg), the diffusing membrane resistance (DmNa) and the two components, diffusing membrane resistance (DmNa) and capillary volume content (Vc). We named LW the lung tissue (mainly water) which is reachable by inspired gases.

Results: As the saponin permeabilization keeps the whole MI population within the cell architecture, the Vmax defines the subject's MI oxidative capacity, the Km (CHF:148 ± 36, SED:111 ± 23, PA:55 ± 10) represents the MI affinity for ADP and the ACR (CHF:3.1 ± 0.5, SED:2.9 ± 0.6, PA:6.5 ± 1.1) defines the phosphorylation-Vo2 coupling efficiency. The Vo2, Vmax and mVo2 are shown on figures. Values: means ± SEM, *p < 0.05 vs CHF.

Conclusion: In CHF patients, the intrinsic SM MI oxidative capacity, MI affinity for ADP and coupling efficiency just reveal untraining, being all similar to the one of SED. This opens the question whether an impaired substrate delivery would represent the main determinant of the abnormal MI exercise metabolism in CHF.

1183-144 High Circulating Levels of Terminal Complement are Associated With Adverse Outcome in Heart Failure

David J. Clark, Michael W. Cienman, Scott A. Rollins, Leonard Bell, Steven E. Patsa, Tahin R. Ramani, Habib Samdani, John F. Sotano. Yale University, New Haven, CT; Alexion Pharmaceuticals, New Haven, CT; Yale University, USA

Background: Terminal complement activation has been linked to myocardial injury and ventricular dysfunction. We previously demonstrated a significant elevation in the levels of serum C5b-9 (sC5b-9), the terminal complement complex, in patients with congestive heart failure (CHF). The purpose of this study was to determine the relationship between the levels of sC5b-9 and clinical outcome.

Methods: We determined 6 month clinical follow up data in a group of 36 patients with NYHA Class III-IV CHF whose original evaluation included ventricular function studies and serum assays for C5b-9 levels. Combined clinical events included death, urgent (Status 1) cardiac transplant, or admission to hospital with worsening heart failure. These patients were stratified into 2 equal groups by using the median sC5b-9 level (highest 50% v slowest 50%).

Results: At entry, the mean left ventricular ejection fraction was 20%. The sC5b-9 levels in these two CHF patients (19±5 ng/ml) were significantly (p < 0.001) elevated compared to healthy controls (20±10 ng/ml). The study population had a 36% (13/36) combined event rate overall at 6 months. Patients in the group with the highest 60% of sC5b-9 levels suffered a significantly higher incidence of clinical events (log-rank test, p = 0.02).

Conclusions: We found that among patients CHF, serum with increased levels of C5b-9 was significantly associated with adverse outcomes at 6 months.

Interaction Between Age and Gender on TNF Levels in Patients With Moderate to Severe Heart Failure

Biyerkem Dozkurt, Dorelyn Lee-Jackson, Adrienne Chee, Anita Deswal, Douglas L. Mann. Baylor College of Medicine, Houston, TX, USA

Previous studies have shown that patients with heart failure (HF) have increased levels of TNF in their circulation. However, the influence of age and gender on TNF levels in HF patients has not been studied. Therefore, we examined baseline TNF levels in 1187 patients with NYHA class III-IV HF.
enrolled in the Veenaraine Trial (VEST). There was a significant linear relationship between age and TNF levels in males (p < 0.001), whereas for females the relationship was dichotomous: TNF levels were modestly elevated in women < 50 yrs (−3.8 pg/ml), whereas strikingly elevated in women ≥ 50 yrs (−7.0 pg/ml).

Conclusion: TNF levels ↑ as a function of increasing age in males with advanced HF, whereas TNF levels ↓ significantly in women with HF ≥ 50 yrs of age. The finding that TNF levels ↑ in women of postmenopausal age with HF is consistent with the fact the estrogen protects against the toxic effects of TNF and estrogen therapy may be beneficial in HF.

The Prognostic Role of Relative Lymphocyte Concentration in Patients With Heart Failure and Low Ejection Fraction

Jalal K. Chali, Susan Anderson, David DeMets, Jay N. Cohn, Cardiovascular Medicine, University of Minnesota, Minneapolis, Minnesota, USA

Background: Extensive work has been focused on the potentially causal role of inflammatory cytokines to the progression of chronic heart failure (CHF). Only little is known on their prognostic value.

Methods: Concentrations of tumor necrosis factor-α (TNFα), soluble TNF receptors (sTNFR1 + 2) and interleukin-6 (IL-6) were studied in 120 CHF patients (103±11 yrs, NYHA III/IV: 73/38/18; age 62 ± 11 yrs, LVEF 30 ± 20%, peak VO2 17 ± 1.1 ml/kg/min, mean ± SE) (min. follow-up 6 months, focus: all-cause mortality).

Results: Of the patients, 44 (37%) died after 0.13-75.1 mos (mean 11.9). In univariate Cox proportional hazard analysis, sTNFR1 + 2, IL-6, total (n = 91) and bioactive (n = 95) TNFα predicted mortality as well as did age (p < 0.001), peak VO2 (p = 0.0001), creatinine (p = 0.0002), NYHA class (p = 0.002) and body weight (p = 0.005). In multivariate analysis, sTNFR1 emerged as the strongest independent predictor of cytokine mortality (all p < 0.01). In stepwise regression, only sTNFR1 (p = 0.0001), age (p = 0.02) and LVEF (p = 0.04) remained significant predictors independently of each other. In receiver operator (ROC) curves, the best mortality predicting concentrations of sTNFR1 were 1460 pg/ml (6 ms, sen 79%, spec 64%); 1460 pg/ml (12/24 ms: sen 71/75%, spec 73/85%, respectively), and 1015 pg/ml (36 ms, sen 90%, spec 98%). The area under the curve for death prediction was consistently larger for sTNFR1 than for peak VO2 at respective time points between 6-36 mos.

Conclusions: Soluble TNFR1 concentrations predict increased long-term mortality in CHF patients independently and more sensitive and specific than other established CHF prognosticators.
A study showed that inducible NOS can contribute to the pathogenesis of Chagas' cardiomyopathy through the release of nitric oxide (NO). The mice infected with the Chagas' cardiomyopathy strain of Trypanosoma cruzi showed an increase in NO production, which was associated with a decrease in cardiac function. The study also found that the NO production was correlated with the severity of myocardial damage, suggesting a role for NO in the progression of the disease.

**Methods:**

- Transthoracic echocardiography was performed to assess cardiac function.
- Histological and immunohistochemical analyses were used to evaluate the distribution of NO synthase (NOS2) and inducible nitric oxide synthase (iNOS).
- Positive topographic correlation was found between reversible defects (RD) and reduced MBG uptake, suggesting a pathogenetic role for these disturbances in CHD.

**Results:**

Positive topographic correlation was found between reversible defects (RD) and reduced MBG uptake, as seen in 81 of 85 segments (96%) containing RD showed abnormal MBG uptake that was seen in only 104 of 573 segments (18%) without RD (Chi-square = 39.719, p < 0.0001).

**Conclusions:** Regional abnormalities of cardiac sympathetic function occur early in the course of Chagas' cardiomyopathy and are topographically related to myocardial perfusion disturbances. These abnormalities tend to aggregate as more severe myocardial damage occurs. Such findings strongly suggest a pathogenic role for these disturbances in CHD.

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**ABSTRACTS – Cardiac Function and Heart Failure 225A**

- **1184-152** Inducible Nitric Oxide Synthase Contributes to Development of Murine Chagas Cardiomyopathy
  - Madhulika Chandra, Stefka B. Petkova, Herbert B. Tanowitz, Vitaliy Shtutin, Laila Z. Escobar, Julian C. Escobar, Zilton A. Andrade, Sujuan Qian, Sonia G. Andrade, William K. Nelson, Moses Sadigursky, Zu-Xi Yu, Victor J. Ferrans. National Institutes of Health, Bethesda, Maryland, USA; Fudacao Oswaldo Cruz, Brazil; University of California, USA

**Background:** Chagas' disease, caused by T. cruzi, is associated with myocarditis, and expression of myocardial cytokines and inducible nitric oxide synthase (NOS2). To assess functional significance of NOS2 in this murine cardiomypathy, and expression of myocardial cytokines and inducible nitric oxide synthase (iNOS), we examined the distribution and expression of iNOS in acute chagasic myocarditis.

**Methods:** Transgenic echocardiography (ATL HDI 5000 cv; 10/5 MHz) was performed in infected WTI (KO) and control WTC (KO) at 10 days post-infection (PI). Repeat studies were performed in surviving KOI (WT) and KOC (WT) at 9 days post-infection.

**Results:** No differences were found at day 10 in left ventricular (LV) wall thickness in diastole (WT, mm), and systolic diameter (EDD, mm), and atrial diameter (ESD, mm), LV fractional shortening (FS%), or qualitative assessment of right ventricular (RV) dilatation (graded from 0 [absent] to 3 [severe]) between KOI and KOC. However, EDD (1.2 ± 0.6 vs 0.8 ± 0.2 cm) and RV (0.6 ± 0.7 vs 0.0 ± 0.0 cm) were larger in WTI v WTC. At day 19, HR was lower in KOI v KOC, without differences in EDD, ESD, WTd, RV or FS% (Table). WTI had larger EDD, ESD, and RV and lower HR and FS% than WTC.

**Conclusions:** The expression of iNOS activity is greatly increased in areas of inflammation in acute chagasic myocarditis, and suggests that this enzyme plays a role in the development of heart failure associated with severe global left ventricular dysfunction, or cardiomyopathy. However, the mechanisms of HIV-related cardiomyopathy has not yet been characterized. We recently examined the effects of an HIV surface envelope protein, glycoprotein 120 (gp 120), on cell contractions and L-type Ca(2+) current and in rabbit ventricular myocytes.

- **1184-154** Effects of HIV Glycoprotein 120 on Cell Contractions and L-Type Ca(2+) Current in Rabbit Ventricular Myocytes
  - Fuhsu Chen, Kevin Shannon, Shulan Ding, Paul Krogstad, Monica Silva, Glenn T. Wetzel, Thomas S. Kitzinger, UCLA School of Medicine, Los Angeles, California, USA

**Background:** The most common and life-threatening cardiovascular complication of HIV infection is the development of heart failure associated with severe global left ventricular dysfunction, or cardiomyopathy. However, the mechanisms of HIV-related cardiomyopathy has not yet been characterized. We recently examined the effects of an HIV surface envelope protein, glycoprotein 120 (gp 120), on cell contractions and L-type Ca(2+) current and in rabbit ventricular myocytes.

**Methods:** Single adult New Zealand ventricular cells were isolated using an enzyme dissociation method. Cells were incubated by electric field stimulation (20-30 volts, 3.5 msec duration, every 3 sec). Intracellular Ca(2+) store-induced cell contraction was induced by a one-second exposure to 10 mM caffeine to extracellular solution to activate the sarcoplasmic reticulum (SR) Ca(2+) release. Whole cell L-type Ca(2+) channel currents were measured using standard voltage-clamp techniques.

**Results:** We found that perfusion with solution containing 0.1 uM of gp 120 significantly inhibited field stimulated contraction (from 5.8 ± 0.5 to 3.9 ± 0.6 pm, mean ± SEM, n = 12, p < 0.01) in isolated rabbit ventricular myocytes (57°C). On the other hand, gp 120 did not significantly decrease the SR Ca(2+) store, or the caffeine-triggered contraction (from 7.4 ± 0.6 to 6.9 ± 0.7 pm, mean ± SEM, n = 12, p = NS). Further, we found that 0.1 uM of gp 120 significantly inhibited L-type Ca(2+) current in rabbit ventricular myocytes (from 6.3 ± 0.8 to 4.3 ± 0.6 pA/pF, n = 8, p < 0.01), as compared with perfusion with buffer alone (from 6.5 ± 0.4 to 6.1 ± 0.0 pA/pF, n = 6, p = NS). Subsequent perfusion with control solution prevented further decrease in the Ca(2+) current.

**Conclusion:** These results show that HIV protein gp 120 inhibits contractions in single cardiac cells, and that this inhibition appears to result from an inhibition of trans-sarcoplasmic Ca(2+) current.

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**1184-155** Onset of Cardiac Symptoms After Mediastinal Irradiation an Ominous Sign Due to Frequently Combined Disease of Coronary Arteries, Heart Valves, Pericardium and Conduction System

- Christine H. Attenhofer Jost, Jurid Turina, Paul R. Vogt, Franz W. Amann, Gabor Stütsch, Rolf Jenni. Division of Cardiology, University Hospital Zurich, Switzerland

**Background:** Significant cardiac complications after radiation therapy (RT) of the mediastinum are rare but can considerably influence long-term mortality in these patients (pts). There are only few data on etiology and prognosis of cardiac symptoms in this pt population.

**Methods:** Since 1990 we evaluated 22 pts in our cardiology division for symptomatic heart disease after mediastinal RT. All pts had a clinical exam, complete 2D – and Doppler echocardiography, and a 12 lead ECG. Data were collected on cardiac catheterizations, cardiac surgery or pacemaker insertion.

**Results:** Age at begin of RT was 37 ± 15 years (yrs), age at last follow-up 58 ± 15 yrs. The RT was administered at different RT centers because of lymphoma (10 pts), breast cancer (9 pts) or other tumors (3 pts). A cardiac dogs were used as controls. Sections of formalin-fixed, paraffin-embedded myocardium were immunostained with a polyclonal antibody against iNOS and a secondary antibody conjugated with fluorescein isothiocyanate. The sections were then processed for the detection of apoptosis by the nick end labeling method (rhodamine-conjugated antibody), counterstained with DAPI to demonstrate the DNA in tissue cells and T. cruzi, and examined by confocal microscopy to evaluate the topographic relationships between the two staining reactions.

**Results:** Apoptosis was most commonly detected in macrophages and lymphocytes, but was also observed in endothelial cells and interstitial den- ular cells in areas of inflammation, as well as in infected and uninfected myocytes. The parasites within some of the infected myocytes gave a positive reaction for apoptosis. Reactivity for iNOS was strong in myocytes and macrophages, in myocytes, the extent of apoptosis in intracellular T. cruzi correlated with an increase in staining (cine) of the parasite.

**Conclusion:** This study shows that iNOS activity is greatly increased in areas of inflammation in acute chagasic myocarditis, and suggests that this enzyme plays a role (by generating nitric oxide) in inducing apoptosis in T. cruzi and host cells. Cytokines, and T. cruzi antigens probably stimulate the production of iNOS in these areas. It is likely that this apoptosis contributes to the cessation of the acute phase of Chagas' myocarditis.
murmur was present in 18 pts (85%), dyspnea on exertion in 18 pts (82%) and angina in 11 pts (56%). A history of heart failure was found in 8 pts (56%). Moderate or severe valvular heart disease was frequent: 6 pts (27%) had aortic stenosis, 5 pts (23%) aortic regurgitation, 4 pts (18%) tricuspid regurgitation, 5 pts (23%) mitral regurgitation. One pt (5%) had mild mitral stenosis. Significant valvular disease was present in 17 pts (77%), significant coronary artery disease (CAD) in 10 pts (45%), disease of the conduction system in 10 pts (45%) and pericardial disease in 6 pts (27%). A combination of at least 2 pathologies was found in 15 pts (68%). Heart surgery was necessary in 8 pts (36%) including coronary artery revascularization, valve replacement, and/or pacemaker surgery. Perioperative care was often prolonged and 2 pts died due to heart failure with severely abnormal diastolic function (25%, mortality). Pacemaker insertion was necessary in 2 pts (9%). Overall, six pts (27%) died 1–4 yrs after PT. Causes of death were: heart failure after heart surgery (2 pts), peripheral arterial emboli with kidney failure (1 pt), heart failure (1 pt), sudden cardiac death (1 pt), and prosthetic valve endocarditis (1 pt).

Conclusions: In the long-term follow-up after medical (H1), onset of cardiac symptoms is often due to a combination of different pathologies of valves, coronary arteries, conduction system or the pericardium. It frequently leads to major cardiac complications including heart surgery and may be the cause of death.

### 1184-156 Prevalence of Effusive Constrictive Pericarditis Among Patients Diagnosed With Constrictive Pericarditis

John H. Hales, Liang H. Ling, Martin E. Bamez, James B. Swarden, Joe K. Oh, Myato Lu, Hoeschen, MN, USA

Background: Pericardial effusion (PE) may be present in patients (pts) with constriction pericarditis (CP) even when requiring pericardiocentesis. Yet, we are unaware of any data regarding the frequency with which PE occurs among the different etiologies of CP and how frequently pericardiocentesis is performed in pts with CP.

Methods: We reviewed the CP database at the Mayo Clinic to determine the frequency by which pericardial effusion (PE) occurs in pts with CP. The database is comprised of all pts diagnosed with CP at the Mayo Clinic from 1985 to 1998. There are 212 pts in the database, 210 of whom have had an echocardiogram.

Results: Fifty-one pts (24%) were found to have a PE (78.4% males with a mean age of 53.7). Table 1 demonstrates the frequency with which PE was noted in association with varying etiologies of CP. Pts with an idiopathic cause as the cause of CP were significantly more likely (p < 0.05) to have PE. No other etiologies were statistically more or less significantly associated with PE.

### Table 1

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Number of cases</th>
<th>Cases w/ effusion</th>
<th>Cases w/o effusion</th>
<th>% cases w/ effusion</th>
<th>Pericarditis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>56</td>
<td>6</td>
<td>50</td>
<td>14%</td>
<td></td>
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<tr>
<td>PVS</td>
<td>48</td>
<td>12</td>
<td>36</td>
<td>25%</td>
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<tr>
<td>Viral pericarditis</td>
<td>34</td>
<td>10</td>
<td>24</td>
<td>29%</td>
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<tr>
<td>Irradiation</td>
<td>25</td>
<td>13</td>
<td>12</td>
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<td>CVC</td>
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<td>3</td>
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<tr>
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<td>0%</td>
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</table>

PCV = previous cardiac surgery; CVD = collagen vascular disease

Of the pts with a PE, 17 (33.3%) underwent pericardiocentesis. These pts had similar symptoms, signs, and long-term survival compared to pts without PE.

Conclusions: Effusive constrictive pericarditis is not uncommon, occurring in 24% of pts with CP. Underlying constriction should be considered in pts presenting with PE and evidence of increased right atrial pressure.

### 1184-157 Increases of Cardiac Troponin I Compared to Creatin Kinase in Acute Pericarditis

Kolend, P., Brandt, Karsten Filzmaier, Uwe Janssens, Peter Hanrath, University Hospital, Aachen, Germany

Background: The diagnostic role of cardiac Troponin I (TnI) is well established in ischemic myocardial injury. The purpose of this study was to compare the serum levels of TnI and creatine kinase MB enzyme (CK-MB) in acute pericarditis.

Methods: We prospectively studied 10 consecutive patients (9 men, 1 woman, age 42 ± 15 years) admitted through the Emergency Department. The diagnosis of acute pericarditis was based on the presence of 3 out of 3 criteria: typical chest pain, pericardial friction rub, and characteristic ECG changes. Significant coronary artery disease was excluded by coronary angiography or exercise stress testing. TnI (normal value < 0.4 ng/ml, fluorometric enzyme immunoassay), and CK-MB (normal value < 6.0 U/L) were measured within 24 hours of symptom onset.

Results: Abnormal values of TnI were noted in 7 out of 10 patients, in whom the average levels were 18.7 ± 18.4 (range 4.6 to 46.7 ng/ml). Six of seven patients with increases in TnI also had elevated CK-MB levels (21.7–12.5 U/L).

Conclusions: Troponin I as a serum marker for myocardial injury is effective in the routine diagnosis of acute pericarditis. TnI is elevated in acute pericarditis with ischemia, however, this marker cannot be used to differentiate acute pericarditis from ischemic myocardial injury. An increase in TnI is slightly more frequent than creatine kinase (i.e., enzyme elevations reflecting the more sensitive nature of Troponin I).

### 1184-158 Post-Operative Cardiac Tamponade in the Modern Surgical Era: Analysis of 4561 Consecutive Patients After Open Heart Surgery

Jeffrey T. Kuvic, Nibal A. Harati, Natesa G. Pandian, Robert M. Bojar, Kamal N. Kheir, Tulane-New England Medical Center, Boston, MA, USA

Background: Pericardial effusions resulting in cardiac tamponade (CT) are uncommon after open heart surgery (OHS) but have been associated with increased morbidity. Characteristics and outcomes of this population are poorly defined.

Methods: This retrospective analysis of 4561 consecutive patients following OHS (1993–1999) examined patients who developed post-operative CT.

Results: Of the 49 patients (1.1%) who died, there were 15 patients who died following cardiac surgery with a pe. The presence of PE in patients with a PE was significantly more likely (p < 0.05) and with a history of irradiation as the cause of CP were significantly more likely (p < 0.05) to have PE. No other etiologies were statistically more or less significantly associated with PE.

### Table 1

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Number of cases</th>
<th>Cases w/ effusion</th>
<th>Cases w/o effusion</th>
<th>% cases w/ effusion</th>
<th>Pericarditis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>258</td>
<td>112</td>
<td>146</td>
<td>44%</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>39</td>
<td>10</td>
<td>29</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Radiation</td>
<td>25</td>
<td>13</td>
<td>12</td>
<td>52%</td>
<td></td>
</tr>
<tr>
<td>CVC</td>
<td>17</td>
<td>3</td>
<td>14</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>10</td>
<td>4</td>
<td>6</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Uremia</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Unspecified</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: CT after OHS is more common following valve surgery and with early postoperative anticoagulation, even when well-controlled. Changes in anticoagulation protocols may reduce the incidence of CT after OHS. When diagnosed and treated promptly, post-operative CT should not increase mortality.

### 1184-159 Are Sporadic Cardiac Myxomas a DNA Repair-Deficient Heart Disease?

John Parissis, 1, 4, George Sourvinos, 1, Flora Sotsios, 1, Spiros Karadas, 4, Dimitrios Spandolis, 1, 2, Medical School of Crete, Heraklion, 2Amalia Fleming Hospital, Athens, Greece

Background: Microsatellite instability (MIN) is an early event in DNA repair-deficient diseases and has been recently described as a possible pathogenetic mechanism of several human tumors, reflecting an attenuated mutator rate in the genome of neoplastic cells. The implication of MIN in pathogenesis of sporadic cardiac myxomas has not been previously investigated.

Methods: To investigate the incidence of MIN in these rare tumors, 11 surgically excised sporadic cardiac myxomas (left atrial; 10, left ventricular) were studied using 30 highly polymorphic microsatellite markers (Research Genetics, Inc. USA) located on a wide range of chromosomal arms. Extracted DNA from myxoma tissue specimens and respective normal myocardial tissue was subjected to polymerase chain reaction (PCR). PCR products were electrophoresed in a 10% polyacrylamide gel and silver stained. MIN was scored by comparing the electrophoretic pattern of the microsatellite markers amplified from paired DNA preparations (tumor/normal tissue). The analysis in the MIN positive cases was repeated at least twice and the results were highly reproducible.

Results: Seven cardiac tumors (64%) exhibited MIN in at least one marker. Five of them were classified as tumors with high MIN (unstable for >2 genetic loci), while the other two as tumors with low MIN (unstable for <2 genetic loci). One tumor exhibited evidence of MIN in 6 markers (extensive genomic instability), while the most frequently affected marker was D17s855 (27%), located on chromosome 17q (within 52 genetic loci). Markers with high instability due to MIN were D17s250 (proximal to D17S1), D17S797 and D17S260. MIN was...
more frequently detectable in chromosome 17 than the other studied chromo-
somes. No association was found between the presence of MIM and the age,
the tumor location or the tumor size.

**Conclusions:** A considerable incidence of MIN was detected in sporadic
cardiac myxomas indicating the presence of a decreased fidelity in DNA repli-
cation and repair in tumor tissue. This observation suggests that sporadic
cardiac myxomas may be a DNA repair-deficient heart disease.

**POSTER**

**1185**

**Cardiac Transplant: Basic Mechanisms**

Tuesday, March 14, 2000, 3:00 p.m.–5:00 p.m.

Anahiem Convention Center, Hall A

Presentation Hour: 4:00 p.m.–5:00 p.m.

**1185-120**

**The Interrelationship Between Myocardial Fibrin, Transplant Coronary Artery Disease, Molecular 1, Cardiac Troponin I and Subsequent Transplant Coronary Artery Disease**

Carlos A. Labarreere, David R. Nelson. Methodist Research Institute, Clarian Health Partners, Indianapolis, IN; Department of Biostatistics and Epidemiology, Cleveland Clinic Foundation, Cleveland, OH, USA

**Background:** The presence of fibrin within the microvasculature and card-
diomyocytes, elevated serum levels of soluble intercellular adhesion mole-
ucle-1 (ICAM-1) and serum cardiac troponin I are all independent risk factors
for subsequent outcome in heart transplant recipients. We studied the inter-
relationship between all these factors and the combined risk for subsequent
transplant coronary artery disease.

**Methods:** Serum soluble ICAM-1 and cardiac troponin I were studied in
serial samples obtained during the first three months after transplantation
(5.3 ± 0.9 Patient) from 128 cardiac allograft recipients using the sandwich
enzyme-linked immunosorbent assay technique. The limit of detection for
serum cardiac troponin I was 0.5 ng/ml. Matching endomyocardial biopsy
specimens were studied immunohistochemically for myocardial fibrin. Serial
consecutive cryosections (0.6–0.4 mm Patient) were studied to evaluate coronary
artery disease.

**Results:** The presence of myocardial fibrin within the first three months fol-
lowing transplantation was significantly associated with serum soluble ICAM-1
levels (p < 0.001). Allograft recipients with myocardial fibrin, elevated serum soluble ICAM-1 and elevated serum cardiac troponin I had respective b/r (95 per-
cent confidence intervals: 3.6–13.0, p < 0.001), 2.7 (95 percent confidence in-
tervals: 1.3–6.6, p = 0.000) and 1.8 (95 percent confidence intervals 1.1–3.0, p
= 0.02) times greater risk to develop coronary artery disease during follow-up.

**Conclusions:** The presence of myocardial fibrin is associated with el-
fibrin deposition on ICAM-1 and elevated serum cardiac troponin I and sub-
sequent coronary artery disease suggesting an activated and procoagulant
microvasculature associates with a worse outcome.

**1185-121**

**Catecholamine Sensitivity Changes With Time After Cardiac Transplantation**

Nicola D. Holt, Kim Fetherington, John H. Dark, Janet M. McComb. Freeman Hospital, Newcastle upon Tyne, UK

**Background:** The denervated transplanted human heart shows presynaptic
β receptor supersensitivity and upregulation which may affect heart rate (HR)
responses. The mechanism of the observed improvement of HR response to
catecholamines following transplantation is not fully known, but changes in catecholamine sensitivity may contribute.

**Methods:** We studied serial changes in catecholamine sensitivity follow-
 ing transplantation in 19 adult recipients at 3, 6, 12, 24 and 52 weeks post
transplant. Intravenous adrenaline (ADR) and noradrenaline (NOR) (6 incre-
mental doses from 0.01 to 0.16 μg/kg) were given and HR response to each
dose measured in beats/min at each time interval.

**Results:** Mean HR response with ADR dose of 0.16 μg/kg and with NOR
dose 0.12 μg/kg (dose limited by diastolic hypertension) were compared

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>3</th>
<th>6</th>
<th>12</th>
<th>24</th>
<th>52</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADR</td>
<td>32.8 ± 6.5</td>
<td>40.5 ± 9.2</td>
<td>47.8 ± 11.7</td>
<td>45.3 ± 9.6</td>
<td>47.3 ± 12.5</td>
</tr>
<tr>
<td>NOR</td>
<td>17.9 ± 6.5</td>
<td>19.5 ± 3.6</td>
<td>21.4 ± 4.4</td>
<td>25.8 ± 6.2</td>
<td>22.3 ± 7.9</td>
</tr>
</tbody>
</table>

**Conclusions:** HR response to both ADR and NOR changed significantly during the first year post transplantation (p < 0.01, ANOVA). HR response to ADR was sig-
nificantly less at 3 weeks compared with 6 weeks and later (p < 0.005, paired t

test, Bonferroni correction); there was no significant change in HR thereafter.
HR response to NOR changed significantly from 3 to 24 weeks and 6 to 12
and 24 weeks (p < 0.005, paired t test, Bonferroni correction) but did not sig-
nificantly change at any other times. Sensitivity to either catecholamine did
not significantly change after 10 weeks.

**Conclusion:** These changes in catecholamine sensitivity may have im-
portant implications for HR response after cardiac transplantation.

**1185-122**

**Urine Fibrinopeptide A as a Risk Factor for Cardiac Events Following Heart Transplantation**

All F. Sorell, Jacqueline O'Connell, Joseph P. McConnell, Kathy Creossilus, Carlos A. Abenson, Nalin Rang, Liron Silvis, Aly Flamen, Vinnyjom I. Prompiki. Clarian Health Partners, Inc., Indianapolis, IN, USA

**Background:** Depletion of arteriolar tissue plasminogen activator and a pro-
coagulant microvasculature are associated with development of transplant
coronary artery disease. We demonstrated the usefulness of fibrinopeptide A
(FPA) in detecting transplant coronary artery disease but the value of FPA in
risk stratifying patients' cardiac events following heart transplantation is not
known.

**Methods:** Urine FPA levels were determined prospectively during outpa-
tient visits of heart transplant recipients. A FPA level ≥ 3.2 ng/mg creatinine
was considered abnormal. Cardiac events studied were mortality, non-fatal
myocardial infarction, development of NYHA class III or IV heart failure, re-
transplantation and restenosis.

**Results:** A total of 73 patients were enrolled in the study and FPA levels
in urine were determined at the time of enrollment. Patients had a mean age of
53 ± 11 years, 79% were males, and they had 6 ± 3 years follow up post cardiac
transplantation at the time of enrollment. Patients were followed for a mean of
0 ± 2 months after enrollment and evaluated for cardiac events. During follow up 14 patients (19%) developed a total of 18 events (2 deaths, 2
non-fatal myocardial infarction, 4 restenotizations and 10 congestive heart
failure). Four of 59 (7%) of event-free patients had abnormal FPA compared
with 14 of 57% of patients with events (p < 0.001). The mean FPA level in
event-free patients was 1.3 ± 0.1 ng/mg creatinine compared to 8.9 ± 4.1
ng/mg creatinine in patients with events (p < 0.0002).

**Conclusions:** Following cardiac transplantation, patients with elevated
FPA are more likely to develop cardiac events compared to those with normal
FPA levels. FPA may be a useful non-invasive marker to stratify patients at
risk following cardiac transplantation and elevated FPA could be associated
with the generation of fibrin within a prothrombogenic microvasculature.
mensen of electrical stimulation (ES) applied for 2 weeks to newly mobilized latissimus dorsi muscle (LDM) may either cause further damage to already ischemic muscle, or be beneficial by promoting recanalization and angiogenesis. We hypothesized that a cautious electrical stimulation protocol would help the muscle recover from ischemia, increase the angiogenic potential, and be beneficial for indirect myocardial recanalization after cardiomyoplasty.

Methods: In this investigation we submitted totally mobilized LDM to ES for 2 months after a 2 week delay. A standard Medtronic protocol was used, however the number of contractions per minute (CPM) were changed: 60 CPM = Series I; 30 CPM = Series II; 15 CPM = Series III. We also added ischemic preconditioning (IPC) with ES applied in the primary culture expressed β-galactosidase 24 hours after recombinant adenovirus transfection. These cells (1 x 10^6) were transplanted into the infarcted rat hearts. 7 days after the transplant, the hearts were removed, and the heart tissue was subjected to direct injection of adenovirus carrying the same reporter gene.

Results: Expression of the β-galactosidase gene in the grafted cells was demonstrated by staining with X-gal, resulting in a blue color. Transgene expression was recognized 7 days after transplantation and was significantly greater than expression achieved by direct injection of adenovirus into myocardial infarction.

Conclusions: Our results demonstrate that ex vivo gene transfer to the infarcted myocardium is feasible and significantly more efficient than direct adenoviral vector mediated gene delivery. Our results suggest that the ex vivo approach may partially eliminate one of the major hurdles facing the application of gene therapy to myocardial infarction.

## ORAL

### 890 Cardiogenic Shock: New Insights and Approaches

**Tuesday, March 14, 2000, 4:00 p.m.-5:00 p.m.**

Anaheim Convention Center, Room 304A

#### 890-T Early Echo-Doppler Findings in Shock Complicating Acute MI

Chi-Ming Chow, Ravin Davidoff, Lisa A. Mondes, Christopher R. Thompson, Lynn A. Sleeper, Richard Steingart, Ken Gin, Vladimir Dzavik, Judith S. Hochman, Michael H. Picard. For the SHOCK Trial Investigators, Massachusetts General Hospital, Boston, MA, USA

**Background:** Restrictive LV filling is assessed by Doppler with associated adverse outcomes or poor survival in subsets of cardiomyopathies. To assess the prevalence and prognostic significance of Doppler patterns in patients with cardiogenic shock (CHS) complicating acute myocardial infarction (AMI), we examined the Doppler patterns patients enrolled in the SHOCK Trial, a multicenter, randomized trial of emergency early revascularization (ERV) as a strategy of initial medical stabilization (IMS).

**Methods:** Transmitral Doppler patterns were examined on baseline echocardiograms upon entry to the study. The parameters examined include peak E and A velocities, deceleration time (DT), time velocity integrals (TVI) of E and A waves, and E/A ratio.

**Results:** A total of 63 baseline echocardiograms were examined (34 ERV, 29 IMS). A wide spectrum of Doppler patterns were observed without difference between the two treatment groups. Mean ± SD values for all 63 patients:

- Peak E (m/s): 0.70 ± 0.32
- Peak A (m/s): 0.67 ± 0.29
- TVI E (m): 0.06 ± 0.04
- TVI A (m): 0.070 ± 0.11
- DT (msec): 129 ± 58

Restricted patterns were common with 47% of patients presenting with C/E ratio > 1.8 and 25% of patients, > 2.3. DT < 115 msec was noted in 24% of patients. There is a trend for higher peak E velocity (>1.0 m/s) to be associated with 30-day survival in the IMS group; OR = 8.25 (p = 0.06). Changes in Doppler parameters over time including comparison of the effects of the treatment strategies on LV filling in addition to hemodynamic correlations will be presented.

**Conclusions:** Although diastolic Doppler filling patterns are diverse, the restrictive filling pattern is common early among patients presenting with CS complicating an AMI. This is suggestive of a high prevalence of elevated LA pressure and poor LV compliance early in this condition.
Short term Results of Left Ventricular Assist and Comprehensive Medical Management as Bridge to Recovery Therapy for Advanced Heart Failure

Marc A. Silver, Mark S. Slaughter, Pat P. Sappap, Antoine J. Tatoolu, Szabolcs Szabo, Heart Failure Institute and Left Ventricular Assist Program, Cleveland Hospital and Medical Center, Oak Lawn, Illinois, USA

Background: Both medical and surgical therapies have been shown to attenuate heart failure (HF) symptoms and improve survival in pts. with advanced HF. Infrequently, and usually only as bridges to heart transplantation, are medical therapies applied in the setting of left ventricular assist. We report short term results of this multidisciplinary approach in unselected pts. with advanced HF.

Methods: Five men, aged 44 to 66 years, with NYHA functional class 4 HF, moderate to severe mitral regurgitation and contraindications to heart transplantation underwent left ventricular assist repair and required LV assist with a Thoratec paracorporeal device. LVAD support was an average of 55 days (range 30 to 116 days). All patients had maximal HF medications uptitrated and also received esoroxic training regimens. Improvement in exercise tolerance (peak VO2), as well as echocardiographic (% fractional shortening), physical, biochemical and neurohormonal markers (plasma norepinephrine, tumor necrosis factor-α) indicated the probability of LV recovery and device weaning proceeded over 7–14 days. At device explantation all patients also received partial left ventriculotomy.

Results: All patients were discharged at 3–5 days post-explant. All 4 pts. are functional class 1 at 11 to 119 (mean 86) days following explantation.

Conclusions: The combination of optimal medical therapy plus mitral valve repair and left ventricular assist applied to patients with advanced HF can provide successful bridge to recovery in unselected patients with desirous ventricular dysfunction, pts with CS may have an improved likelihood of survival.

Improved Survival Following Acute Myocardial Infarction Complicated by Cardiogenic Shock With LVAD/Transplant Support: A Study Comparing Aggressive Intervention With Conservative Treatment

Waikas Tayara, Randall C. Starling, James B. Young, Osama Wazni, Fouad J. Jubran, Nicholas Smedira, Patrick McCarthy, Cleveland Clinic Foundation, Cleveland, Ohio, USA

Background: While the prognosis for patients (pts) with myocardial infarction (MI) has steadily improved, it remains poor for those developing cardiogenic shock (CS). With advancements in mechanical circulatory support and revascularization, pts with CS may have an improved likelihood of survival.

Methods: We analyzed 138 consecutive cases at the Cleveland Clinic from 1992–1998 who met the institutional criteria for CS following MI to determine the effect of treatment modality on outcome. All pts received intensive medical therapy (IMT) and IABP support. While 95 pts were treated with aggressive interventions (percutaneous intervention (PCI), CABG, heart transplantation or left ventricular assist device (LVAD)), 43 remained on IMT alone (conservative group).

Results: The two groups were comparable for baseline characteristics. The effect of revascularization, transplantation or LVAD, as well as conservative treatment, to improve hemodynamic support and improve outcome, the in-hospital survival were evaluated (Table). N Morbidity N Morbidity

<table>
<thead>
<tr>
<th>Overall</th>
<th>138</th>
<th>62% (86/138)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conservative</td>
<td>43</td>
<td>81% (35/43)</td>
</tr>
</tbody>
</table>
| Aggressive | 95 | 24% (23/95) | 0.0005
| PC or CABG | 92 | 60% (55/92) | 0.0004
| Transplant/LVAD | 17 | 29% (5/17) | 0.022

p-values represent comparison with conservative group.

Conclusions: These data suggest that an aggressive interventional strategy, particularly cardiac transplantation, improves survival in pts with CS. Overall mortality was 62%, it was highest in the conservative group (81%) and lowest among the most aggressively treated pts with transplant/LVAD (29%).

L-NMMA (A Nitric Oxide Synthase Inhibitor) is Effective in the Treatment of Cardiogenic Shock

Gad Coster, Edo Kuhlau, Alex Blatt, Olga Milovanov, Yaron Moshovitz, Nicot Zaidenstein, Ah Salah, Daniela Alon, Michael Meltzer, Zvi Vened, Ahuva Golik, Assaf-Harofeh Medical Center, Zerifin, Israel

Objective: To assess the safety and efficacy of L-NMMA (a nitric oxide synthase inhibitor) in the treatment of cardiogenic shock.

Methods: Eleven consecutive patients with refractory cardiogenic shock were enrolled in this study. All patients underwent coronary catheterization and primary PTCA when feasible upon admission and coronary catheterization. Pints were excluded if not having refractory cardiogenic shock for >24 hours from admission despite treatment with mechanical ventilation, intraaortic balloon pump (IABP) and high doses of catecholamines, and if deemed beyond treatment by two expert cardiologists. L-NMMA (Clin-Alpha, Cel-Blochrem) was administered as an intravenous bolus of 1 mg/kg/hr continuous for 5 hours. Treatment with fluids, catecholamines, mechanical ventilation, and IABP was kept constant throughout the study.

Results: Within 5–10 minutes of L-NMMA administration, mean arterial blood pressure increased from 75 ± 9 to 106 ± 19 mmHg (+41%). During L-NMMA administration urine output increased from 65 ± 20 cc/hr to 158 ± 67 cc/hr (+132%). Cardiac index decreased within 1 hour (during the steep increase in blood pressure and photothermo) from 2.0 ± 0.6 to 1.7 ± 0.1 (min/m² (-15%) however it gradually decreased to 1.4 ± 0.5 (min/m²) after 5 hours of treatment. The heart rate as well as the wedge pressure remained stable. Twenty-four hours following L-NMMA discontinuation MAP (104 ± 10 mmHg (+35%)) and urine output (186 ± 78 cc/hour (+174%)) remained increased, however wedge pressure and cardiac index returned to pre-treatment level. No adverse events, new ischemia, nor arrhythmias were detected. Ten out of 11 patients could be weaned off mechanical ventilation and IABP. Eight patients were discharged from the coronary ICU and seven are alive at 1 month follow-up.

Conclusion: L-NMMA administration has favorable clinical and hemodynamic effects on patients in cardiogenic shock.
Conclusions: A novel method for the treatment of HF has been demonstrated showing significant improvement of hemodynamic parameters during the application of CCM signals. Further studies are planned to optimize the CCM signal parameters in different clinical settings and for different pathological conditions.

9:01-2 Left Ventricular Pre-Excitation Improves Mechanoenergetics of Patients With Dilated Cardiomyopathy and Ventricular Conduction Delay
Gregory S. Nelson, Ronald D. Berger, Barry J. Felts, Maurice Talbot, David A. Kass. The Johns Hopkins Hospital, Baltimore, Maryland, USA

Background: Left ventricular or bi-ventricular pre-excitation of the left heart by VDD pacing improves systolic function in patients with dilated cardiomyopathy (UCM) and asynchrony was measured associated with vent runcus branch block (LBBB). This is achieved at an unaltered heart rate largely due to improved myocardial oxygen demand (MVO2). VDD pacing acquires systolic benefits with minimal energetic cost.

Methods: Eight DCM patients with LBBB (LV ejection fraction: 20.9 ± 6.3%; QRS duration: 176.0 ± 9.8 ms, mean ± SD) underwent catheterization with a dual-sensor micromanometer catheter to measure proximal aortic and LV pressures, an Intracardiac Doppler wire to assess mean coronary flow (FCor), and arterial-coronary sinus oxygen difference (AVO2) sampling. Mean QCor × AVO2 was used to index relative changes in MVO2. Data were compared between normal anatomic rhythm, VDD pacing in a lateral coronary, and LBBB. The latter triggered to match dP/dt, change with pacing.

Results: VDD pacing enhanced dP/dt, 42.9 ± 15.3% (n = 8, P < 0.001) and pulse-pressure 19.8 ± 11.0% (n = 7, P = 0.002). In 78 patients, MVO2 decreased 10.8 ± 8.6% (P = 0.03), AVO2, 4.5 ± 4.0% (P = 0.02) and mean QCor – 6.3 ± 10.7% (NS). In the one patient whose MVO2 increased, dP/dt, rose 77% and pulse-pressure 39%, a contractile response which was nearly twice the mean. By sequential subtraction, Juxtaposition increased dP/dt, similar to pacing (37 ± 15%: n = 7, P = 0.002). However, unlike pacing, dobutamine increased MVO2, 39.6 ± 41.1% (P = 0.005 versus pacing).

Conclusion: VDD pacing may be an attractive alternative to conventional DCM therapy in this patient group because it enhances systolic function while at the same time generally decreasing the energy requirements of the failing heart.

9:00 a.m.

9:01-3 Long-Term Benefit of Cardiac Resynchronization in Heart Failure Patients: The 12 Month Results of the InSync Trial
Daniel Gras, Serge Cazeau, Philippe Mabo, Cliff Bucknall, Anthony S.L. Tang, Henrik Dusek Lutfi, Anders Kierstein-Pedersen, Eric M. Dvorak, Michael A. Kass. The Johns Hopkins Hospital, Baltimore, Maryland, USA

Background: The InSync clinical study is a prospective, multi-center, longitudinal trial evaluating cardiac resynchronization therapy in patients (pts.) with advanced heart failure (NYHA Class III/IV), dilated cardiomyopathy (EF ≤ 35%, LVEDD ≥ 60 mm) and ventricular conduction abnormalities (QRS > 150 ms).

Methods: 102 pts. implanted with the InSync system, including a transvenous left ventricular lead via the coronary veins, were included in this analysis. Clinical endpoints were compared between baseline and last follow-up for groups defined as responders and nonresponders based on improvements in NYHA class, quality of life (≥ 30), and 6 min walk distance (≥ 100 m).

Results: Comparing outcomes for responders (N = 72 pts.) defined as pts. with improvement in NYHA class, the results were improvement in quality of life [23 ± 24 vs 0 ± 24, p < 0.005], shortening of QRS duration [31 ± 61 ms vs – 11.1 ± 21 ms, p < 0.05], improvement in LVEF%[2.5 ± 9.7% vs – 6.0 ± 0.7%, p = 0.006] and decrease in LVEDD [75.1 ± 6.5 mm vs – 1.5 ± 3.7 mm, p = 0.007]. Comparing outcomes for responders (N = 60 pts.) defined as pts. with improvements in one of three endpoints, the result was significant shortening of QRS duration [29 ± 32 ms vs – 14 ± 19 ms, p < 0.05]. Comparing outcomes for responders (N = 35 pts.) defined as pts. with improvements in two of three endpoints, the results were significant shortening of QRS duration [45 ± 7 ± 36 ms vs 0 ± 2.3 vs ± 7.5%, p < 0.05].

Conclusions: Responders to cardiac resynchronization therapy had consistent shortening of QRS duration. Dependent on the definition of responder, improvements were also observed in quality of life, LVEF% and LVEDD. These results suggest that cardiac resynchronization provides functional improvement in heart failure patients. Randomized control studies will provide further information regarding the efficacy of cardiac resynchronization therapy and appropriate patient selection for this therapy.

9:15 a.m.

9:01-4 Responders and Nonresponders to Cardiac Resynchronization Therapy: Results From the InSync Trial
Daniel Gras, Philippe Mabo, Cliff Bucknall, Anthony S.L. Tang, Henrik Dusek Lutfi, Anders Kierstein-Pedersen, Eric M. Dvorak, Michael A. Kass. The Johns Hopkins Hospital, Baltimore, Maryland, USA

Methods: 102 pts. implanted with the InSync system, including a transvenous left ventricular lead via the coronary veins, were included in this analysis. Clinical endpoints were compared between baseline and last follow-up for groups defined as responders and nonresponders based on improvements in NYHA class, quality of life (≥ 30), and 6 min walk distance (≥ 100 m).

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Conclusions: Responders to cardiac resynchronization therapy had consistent shortening of QRS duration. Dependent on the definition of responder, improvements were also observed in quality of life, LVEF% and LVEDD. These results suggest that cardiac resynchronization provides functional improvement in heart failure patients. Randomized control studies will provide further information regarding the efficacy of cardiac resynchronization therapy and appropriate patient selection for this therapy.

9:30 a.m.

9:01-5 Improvement in Left Ventricular Performance by Enhanced External Counterpulsation in Patients With Heart Failure
John Gorcsan III, Lawrence Crawford, Ozlem Soran, Hao Wang, Donald Sevveryn, Paul-Andre de Lame, Virginia Schneider, Arthur M. Feldman, University of Pittsburgh, Pittsburgh, PA, USA

Background: Enhanced external counterpulsation (EECP) is a novel noninvasive therapy consisting of gated diastolic sequential leg compression producing similar hemodynamic effects as an intra-aortic balloon pump. Although preliminary data suggest that EECP has favorable effects on exercise capacity in patients with heart failure (HF), its effects on LV function has not been characterized.

Methods: To test the hypothesis that EECP may have beneficial effects on LV performance in HF, 8 patients with NYHA Class II or III HF and ejection fraction (EF) < 40% were studied. Preload-adjusted maximal power (PAMP) was assessed as a relatively load independent measure of LV performance before and after EECP treatment consisting of 35 ± 1-hr sessions over 7 weeks. Medical therapy was unaltered during this time. Pressure volume relations were simultaneously estimated using echocardiographic automated border detection as a surrogate for LV volume and photoplethysmography as a surrogate for LV ejection pressure to obtain rate-predicted PAMP noninvasively.

Results: Significant increases in PAMP were observed after EECP therapy from 4.2 ± 1.6 to 5.4 ± 2.0 mW/cm²; p < 0.05 vs. baseline. EF also increased from 28 ± 10 to 39 ± 8% and heart rate decreased from 73 ± 6 to 65 ± 5 min⁻¹; p < 0.01 vs. baseline.

Conclusions: EECP therapy was associated with improvements in PAMP and EF along with decreases in heart rate in these HF patients. EECP appears to be beneficial to LV function in HF patients and may be a useful adjunct to medical therapy.
Background: Exercise training has been shown to augment functional work capacity in particular by peripheral adaptations in patients (pts.) with stable chronic heart failure (CHF), whereas effects on central hemodynamics remain contradictory. The Leipzig Heart Failure Training Trial is a large prospective monocenter study to evaluate the effects of long-term exercise training in pts. with CHF on left ventricular function and hemodynamic response to exercise.

Methods: 79 pts. with CHF due to dilated cardiomyopathy (n = 61) or ischemic heart disease (n = 12) were prospectively randomized to either a training group (T) (n = 36; left ventricular ejection fraction by ventriculography ≤ 35%) or a similarly matched control group (C) (n = 43; LV-EF ≥ 35%; 2%). At the study begin and after 6 months pts. underwent symptom-limited ergospirometry with measurement of central hemodynamics by thermodilution and echocardiography with determination of the LV volumes and sphericity indices (longitudinal/transverse LV-diameter).

Results: After 6 months, a reduction in systemic vascular resistance (SVR) at peak exercise by 20% was observed in T (from 770 ± 71 to 613 ± 41 dyne·sec·cm⁻²; p < 0.01 vs. C) and an increase in LV stroke volume by 15% (from 95 ± 9 to 109 ± 8 mL; p < 0.05 vs. C). There was a small but significant reduction in left ventricular end-diastolic diameter (LVEDD) by 6% (from 69 ± 6 to 65 ± 2 mm; p < 0.001 vs. C) and an increase in LV-EF by 17% (30 ± 2 to 35 ± 2; p < 0.01 vs. baseline). Changes in SVR at rest were correlated with changes in SV (r = -0.70; p < 0.001) and changes in LVEDD (r = 0.45; p < 0.01). In T LV end-systolic sphericity index increased from 1.40 ± 0.05 to 1.50 ± 0.05 (p < 0.05 vs. C).

Conclusion: In pts. with CHF long-term exercise training is associated with a considerable afterload reduction. This beneficial training effect results in a small, but significant reduction in cardiomegaly, improvement of left ventricular geometry and cardiac function.

MODERATED POSTER SESSION

1010 Cardiac Function in Health and Disease
Wednesday, March 15, 2000, 9:00 a.m.–11:00 a.m.
Anaheim Convention Center, Hall A

1010-167 β-Adrenergic Blockade in Developing Heart Failure: Effects on Mycocardial Inflammatory Cytokines, Nitric Oxide, and Remodeling
Sumanth D. Prabhu, Bysani Chandrasekar, David P. Murray, Gregory L. Freeman, UT Health Science Center and South Texas Veterans Health Care System – Audie Murphy Division, San Antonio, Texas, USA

Background: Whether β-adrenergic blockade modulates expression of inflammatory cytokines and nitric oxide (NO) in failing myocardium is not known. We examined the effects of chronic metoprolol administration on chamber remodeling, myocardial TNF-α, IL-1β, and IL-6 expression, and NO during the development of left ventricular (LV) dysfunction induced by left coronary artery ligation in the rat.

Methods and Results: Two weeks after ligation in untreated rats, echocardiography and LV weight revealed significant LV dysfunction, systolic dysfunction, and hypertrophy compared to sham (p < 0.001). Papillary muscle studies revealed isoproterenol hyporesponsiveness unaltered by NO synthase (NOS) inhibition. Cardiac inducible NOS (iNOS) mRNA in non-ligated regions and circulating NO metabolites were undetectable. Myocardial TNF-α, IL-1β, and IL-6 mRNA and protein were markedly elevated compared to sham (p < 0.001), with two-fold higher expression (p < 0.025) of IL-6 compared to TNF-α and IL-1β. Metoprolol administration starting 48 hours after ligation resulted in: 1) less LV dysfunction, hypertrophy, and systolic dysfunction (p < 0.02); 2) preservation of the isoproterenol response (p < 0.025) via NO-independent mechanisms, and 3) reduced myocardial gene expression and protein production of TNF-α and IL-1β (p < 0.05) but not IL-6, which remained markedly elevated. The degree of mRNA expression of TNF-α and IL-1β, but not IL-6, correlated well with the degree of LV hypertrophy, regardless of metoprolol.

Conclusions: During heart failure development, adrenergic activation contributes to increased myocardial expression of TNF-α and IL-1β, but not IL-6, and one mechanism whereby β-adrenergic blockade improves myocardial function and remodeling may be related to attenuation of TNF-α and IL-1β expression, independent of NOS and NO.
Change in Diastolic Left Ventricular Function After One Year of Anthypertensive Treatment: The LIFE Study

Kriellan Wachtell, Jonathan N. Bella, Jens Rolstedal, Vaasilio Papademetriou, Bjorn Dahlb, Tapio Alto, Eva Gerlitz, Richard B. Devereux, Glostrup University Hospital, Glostrup, Denmark; The New York Hospital-Cornell Medical Center, New York, USA

Background: We have previously reported that patients with left ventricular (LV) hypertrophy (LVH) have impaired diastolic function and that this was associated with LVH. It remains unclear what impact antihypertensive treatment and LV mass reduction have on the prevalence of LV diastolic function.

Methods: Doppler echocardiograms were recorded at baseline in unmedi- cated patients with stage I–III hypertension and LVH determined by ECG (Cor- nell voltage duration > 2.44 mV) or Sokolow Lyon: SV1 + RV5 + Rv6 = 38 mm after 14 days of placebo treatment; follow-up echocardiograms were done after 1 year of targeted treatment with either losartan or atenolol, and in some cases supplemented with thiazide and calcium antagonist in order to reach target blood pressures (BP) of 140/90 mmHg.

Results: In 711 patients needed diastolic measurements, systolic BP (SBP) was reduced from an average 174 ± 21 to 150 ± 50 mmHg, dia- tolic BP (DBP) from 55 ± 11 to 84 ± 10 mmHg, LV mass was reduced from 234 ± 56 to 207 ± 50 g (p < 0.001). Decrease in isovolumetric relaxation time was related to reduction in LV mass (r = 0.10G) and relative wall thickness (RWT) (r = 0.154, both p < 0.001), but was not related to the decrease in either SBP or DBP (NS). Decrease in RWT and SBP did not correlate to increased E/A-ratio, whereas LV mass changes did not (NS). Normal LV filling increased from 15 to 28%, abnormal relaxation decreased from 67 to 57%, pseudonormalization from 10 to 5% and restrictive filling pattern remained at 4%. However, most patients retained some or abnormal mitral flow pattern.

Conclusion: Twelve percent LV mass reduction through antihypertensive therapy normalizes LV filling parameters in 20% of patients, while 10% de- velop LV filling abnormalities and 69% remain unchanged. One year of treat- ment might not be long enough time to normalize LV diastolic filling in majority of patients.

Evaluation of Global Left and Right Ventricular Function during Supine Physical Exercise by Ultra-Fast Magnetic Resonance Imaging

Arno A.W. Roest, Patrik Kunz*, Hildo J. Lamb, Willem A. Helbing*, Ernst E. van der Wall, Albert de Roos, "Interuniversity Cardiology institute of the Netherlands, Utrecht, The Leiden University Medical Center, The Netherlands

Background: Cardiac response to physical exercise may be impaired in pa- tients with heart disease and can be abnormal in the absence of clear symp- toms at rest. Magnetic resonance imaging (MRI) is an excellent tool to eval- uate ventricular function, especially at the right ventricle. However, assessment of ventricular response to physical exercise by MRI is difficult due to increased motion artifacts during exercise. Aim of this study was to evaluate left (LV) and right (RV) ventricular response to supine physical exercise with the application of a ultra-fast MRI sequence.

Methods: Ventricular function at rest and during exercise was studied in 15 healthy volunteers using an ultra-fast turbo field echo planar imaging MRI sequence. Individual exercise levels were based on the workload at 60% of the prior measured maximal oxygen uptake. Exercise was performed on a MRI compatible ergometer. Ten slices in the short-axis direction covered both left and right ventricle and were obtained using 5 breath-holds, Each breath-hold was performed during an 8-heartbeat suspension of exercise and in this period a 2 short-axis slices were acquired.

Results: Ejection fraction (EF) of the LV and the RV increased in all vol- umes in response to exercise: LV: 12 ± 6%; RV: 10 ± 4%. Furthermore, increase in stroke volume (SV) from rest to stress of the LV (15 ± 9 ml) and the RV (14 ± 7 ml) was observed in all subjects. For the LV, increase in EF and SV was the result of a combined decrease in end-systolic volume (ESV) (−20 ± 11 ml) and end-diastolic volume (EDV) (−6 ± 10 ml). Whereas for the RV, increase in EF and SV was the result of a decrease in ESV (−19 ± 10 ml).

Conclusions: This study shows that it is feasible to evaluate cardiac re- sponse to supine physical exercise in healthy subjects with an ultra-fast MRI sequence. In agreement with literature, SV and EF of both ventricles increased in response to exercise mainly due to a decrease in ESV.

Angiotensin-Converting Enzyme Inhibitor Use in Diastolic Heart Failure is Associated with a Reduced Risk of Death

Edward F. Philbin, Thomas A. Rocco, Jr., Norman W. Lindenmuth, Paul J. Jenkins, Henry Ford Hospital, Detroit, MI; Unity Health System, Rochester, NY, USA

Background: The role for angiotensin-converting enzyme inhibitor (ACEI) use in patients with heart failure (HF) and abnormal left ventricular (LV) systolic function is established. The utility of ACEI among HF patients with preserved function is unknown. This study examined the association between ACEI use and clinical outcomes among a group with HF and normal LV systolic function.

Methods: From a registry of 2,906 consecutive patients with confirmed HF admitted to 10 hospitals, we identified 1,694 with measurement of LV function. Of these, 791 were hospital survivors, had LV systolic function (EF) ≥ 40% or normal contractility and were followed prospectively for 6 months after discharge.

Results: Median age was 75 years; 66% were women. Mean EF was 51 ± 9%. ACEI were prescribed to 368 of 721 (53%) (ACEI+) at hospital discharge; 339 (47%) were discharged without ACEI (ACEI−). Compared with ACEI−, ACEI+ had lower EF (45 ± 8% vs. 62 ± 9%, P = 0.0002) and lower serum creatinine (1.4 ± 1.2 vs. 1.8 ± 1.8, P = 0.01). ACEI+ were more likely to receive digoxin, diuretics and warfarin, but less likely to receive calcium blockers (all P < 0.05). Mean hospital length of stay (7.2 vs. 7.0 days), hospital charges ($7,777 vs. $8,096) and NYHA functional class 1 month after discharge (2.3 vs. 2.1) were similar for ACEI+ and ACEI− (all P > 0.05).

Crude death and hospital readmission rates are shown in the Table. Logistic regression was used to account for baseline differences between the groups; adjusted odds ratios (OR) and confidence intervals (CI) are also shown in the table. As shown, mortality was lower among ACEI+ than hospital readmission rates also favored ACEI+ but the differences were not statistically significant.

Conclusions: In patients with HF treated in the community setting, ACEI use among the sizeable subset with preserved LV systolic function is associ- ated with reduced mortality and a trend for fewer hospital admissions. Large, prospective, randomized, controlled trials are now required to confirm these interesting but preliminary and hypothesis-generating results.

Omapatrilat Improves Volume Homeostasis in Chronic Heart Failure

Dougal R. McClean, Hamid Ilkem, Ian G. Crozier, Michelle Reynolds, A. Mark Richards, M. Gary Nicholls, Christchurch Hospital, Christchurch, New Zealand

Background: Omapatrilat is a new compound that simultaneously inhibits angiotensin converting enzyme (ACE) and neutral endopeptidase. We examined if effects of chronic vasopeptidase inhibition (VPI) on volume home- stasis in patients, with symptomatic heart failure are different from ACEI.

Methods: Nineteen patients with NYHA class II–III and LVEF ≤ 40% were randomised to one of five omapatrilat doses for 12 weeks. Diuretics were not increased over 12 weeks. Blood volume using indocyanine green dye method, venous blood for ANP and left ventricular volumes using echocardiography were measured at baseline and after 12 weeks, 24-hour urinal volume and sodium excretion was measured on day one and day 83. Data is presented as mean ± SEM.

Results:

<table>
<thead>
<tr>
<th>Changes at 12 weeks</th>
<th>Low dose (n = 10)</th>
<th>High dose (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Volume (ml)</td>
<td>44 ± 249</td>
<td>-749 ± 194</td>
</tr>
<tr>
<td>Urine Volume (ml)</td>
<td>18 ± 218</td>
<td>398 ± 113</td>
</tr>
<tr>
<td>Urine Sodium (mmol)</td>
<td>2 ± 17</td>
<td>41 ± 12</td>
</tr>
<tr>
<td>End Diastolic Volume (EDV)(ml)</td>
<td>11 ± 10</td>
<td>15 ± 8*</td>
</tr>
<tr>
<td>End systolic volume (ESV)(ml)</td>
<td>42 ± 2</td>
<td>-243 ± 3**</td>
</tr>
<tr>
<td>Ejection Fraction (%)</td>
<td>2.5 ± 2.1</td>
<td>7.1 ± 1.2</td>
</tr>
<tr>
<td>Plasma ANP (pmol/L)</td>
<td>3.9 ± 6.8</td>
<td>38.3 ± 14.8</td>
</tr>
</tbody>
</table>

Change in Blood Volume was correlated with change in ESV (r = 0.64; p < 0.01), and change in urine volume (r = -0.64; p < 0.01), n = 0.05 and "p = 0.01 vs. low dose group"

Conclusions: High dose chronic omapatrilat therapy produces beneficial changes in patients with chronic heart failure by reductions in left ventricular and circulating blood volumes coupled with potentiation of natriuretic peptide
and natriuresis at 12 weeks. Further studies are needed to compare these changes with selective ACE inhibition alone.

**1010-174**

**Better Systolic Function, But No Better Survival, for Women With Advanced Heart Failure: Findings From the Duke Databank for Cardiovascular Disease**

Monica R. Shah, Linda Shaw, Christopher M. O'Connor, Robert M. Califf. Duke Clinical Research Institute, Durham, NC, USA

**Background:** Women with heart failure (HF) may have a higher rate of preserved systolic function than men with HF; however, this does not translate to improved survival. We prospectively studied 1344 patients to identify the distribution by sex of heart failure with preserved systolic function vs. systolic dysfunction, and the effects of systolic function and gender on survival over 2 years.

**Methods:** We identified 693 women and 681 men with Class IV HF symptoms from the Duke Cardiovascular Databank. Those with an ejection fraction (EF) >59% on ventriculography were considered to have preserved systolic function.

**Results:** Women with advanced HF were more often hypertensive (68.5% vs. 63.1%; p = 0.039), more likely to have preserved systolic function (64.9% vs. 40.8%; p < 0.001), and had a higher EF (median 50% vs. 35%; p < 0.001). Women were less likely to have ischemic cardiomyopathy (64.7% vs. 73.7%; p < 0.001). A Cox model showed no significant difference in mortality between women and men at 5 years, even after adjusting for age, preserved systolic function, and etiology of HF.

**Conclusions:** Women with Class IV heart failure symptoms are more likely to have preserved systolic function. Despite this, and despite having a lower rate of ischemic cardiomyopathy and higher ejection fractions, women with advanced heart failure die at a rate similar to that of men with this disease.

**1010-175**

**Passive Ventricular Constraint in Advanced Heart Failure Prevents a Further Decline in Cardiovascular Function**

John M. Power, Jai Raman, Melissa Byrne, Cliff Alferness. University of Melbourne (A&FMC Campus), Heidelberg, Australia

**Background:** Passive ventricular constraint in early experimental heart failure has been shown to halt the progression to advanced heart failure associated with dilated cardiomyopathy. We examined the efficacy of this treatment in advanced heart failure.

**Methods:** A Transonic 30A cardiac output (CO) flowprobe was implanted in the pulmonary artery of 12 adult men. The animals were paced at 180-190 bpm for 21 days and then 49 days to 200-210 bpm to induce advanced heart failure. In 8 animals an Acorn cardiac support device (Acorn Cardiovascular Inc, St Paul MN) was implanted, via a partial sternotomy, around both ventricles. Prior to revascularization, the hearts were recommenced for a further 28 days in animals. Cardiovascular parameters were determined using echocardiography and a submaximal treadmill exercise protocol at baseline. In advanced failure and at termination of pacing.

**Results:** Left ventricular function was significantly depressed in all animals in advanced failure in comparison with baseline and continued to decline in non-implanted animals over the additional 4 weeks of pacing. However, in the implanted animals deterioration was arrested or significantly improved in comparison with implants.

**Group**

<table>
<thead>
<tr>
<th>LV + dP/dt (ma)</th>
<th>No Implant</th>
<th>Acorn (Implant)</th>
<th>Acorn (Implant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Implant</td>
<td>1096</td>
<td>1146</td>
<td>992</td>
</tr>
<tr>
<td>Acorn (Implant)</td>
<td>1537</td>
<td>1310</td>
<td>1128</td>
</tr>
</tbody>
</table>

**Conclusion:** In this animal model of advanced heart failure preserved ventricular constraint was able to reverse the deterioration in cardiovascular function observed in control animals.
data suggest that ACE inhibition may prevent remodeling of the infarcted heart in part by a modulation of the expression of protein kinase C.

**1206 143 Enhanced Angiotensin II Type 2 Receptor mRNA and Protein Expression During Cardioprotection Induced by Receptor Blockade During Ischemia-Reperfusion in Isolated Working Rat Hearts**

Both I. Juddt, Yi Xu, Alexander S. Cianchian. University of Alberta, Edmonton, Alberta, Canada

**Background:** We hypothesized that improved recovery of mechanical function after ischemia-reperfusion (IH) induced by acute angiotensin II (AngII) type 2 receptor (AT$_2$R) blockade is an AT$_2$R-mediated effect that is associated with AT$_2$R upregulation.

**Methods:** We assessed changes in AT$_2$R and AngII type II receptor (AT$_2$I, R) expression (immunoblots) in isolated working rat hearts subjected to 30 min global ischemia and 30 min reperfusion. Groups of adult hearts (n = 6) were exposed to no drug/no IR (control), IR and IR plus the AT$_2$R antagonist PD 123,319 (PD, 0.3 mmol/l). Immunostaining for hBNP was present in myocytes and non-myocytes in PD-treated animals. hBNP mRNA and protein but did not change AT$_2$R mRNA or protein.

**Results:** Compared to controls, IR reduced recovery of LV work and downregulated AT$_2$R mRNA and protein, and AT$_2$R mRNA (not protein). In contrast, PD improved recovery of LV work after IR (0.85 vs 0.58 p = <0.001) and upregulated AT$_2$R mRNA and protein but did not change AT$_2$R mRNA or protein.

**Conclusion:** The results suggest that PD-induced cardioprotection in acute IR is AT$_2$R-mediated.

**1206-144 Systemic and Myocardial Expression of Brain Natriuretic Peptide After Adenoviral-Mediated Gene Transfer Using a New Catheter-Based Approach**

Dirgit Kenter, Robert G. Schwartz, Cheri S. Mueske, Laurel S. Kleppe, Denise Heubel, Maria Palatsi, John C. Burnett, Robert D. Simari. Mayo Clinic and Foundation, Rochester, Minnesota, USA

**Background:** Brain natriuretic peptide (BNP) is a potent natriuretic, diuretic, and vasoactive hormone produced and released by cardiomyocytes. In heart failure, plasma BNP levels increase and may be protective in early stages of the disease. We investigated whether intramyocardial injection of an adenovirus expressing human BNP (hBNP) in dogs would result in local myocardial expression and secretion of mature BNP into the systemic circulation.

**Methods:** We investigated whether intramyocardial injection of an adenovirus expressing human BNP (hBNP) in dogs would result in local myocardial expression and secretion of mature BNP into the systemic circulation. We hypothesized that improved recovery of mechanical function after ischemia-reperfusion (IH) induced by acute angiotensin II (AngII) type 2 receptor (AT$_2$R) blockade is an AT$_2$R-mediated effect that is associated with AT$_2$R upregulation.

**Results:** Compared to controls, IR reduced recovery of LV work and downregulated AT$_2$R mRNA and protein, and AT$_2$R mRNA (not protein). In contrast, PD improved recovery of LV work after IR (0.85 vs 0.58 p < 0.001) and upregulated AT$_2$R mRNA and protein but did not change AT$_2$R mRNA or protein.

**Conclusion:** The results suggest that PD-induced cardioprotection in acute IR is AT$_2$R-mediated.

**1206-145 Possible Molecular Mechanisms Responsible for the Beneficial Effects of Physical Training on Cardiac Function During Development of Heart Failure**

Jie Wang, Gong-xia Yu, Bo-lin Cai, Andrew R. Marks, Lu Lu, David E. Gutstein. Columbia University, New York, New York; Mt. Sinai Medical Center, New York, New York, USA

**Background:** We Previously reported that daily physical training (PT) preserved cardiac function during development of heart failure (HF). The cardiac sarcolemmal nestin reductase ATPrev (SEPCA2a), Nha $\cdot$ Ca$^{2+}$ Exchanger (Exchanger) and natriuretic peptide receptor (NPYR2) are proteins involved in regulating myocyte Ca$^{2+}$ homeostasis and maintaining normal cardiac function. The goal of this study is to test whether hBNP alters these proteins during development of HF.

**Methods:** Left ventricular (LV) samples were obtained for mRNA level (northern analysis, band intensities normalized to GAPDH) and protein level (Western Analysis, band intensities normalized to tubulin) from 5 groups of dogs: normal dogs; 5 dogs with cardiac pacing-induced HF (210 bpm for 3 wks, 240 bpm for the 4th wk) and 5 dogs with the same cardiac pacing regimen plus daily PT (5 ± 2.2 km/hr, 2 hours/day).

**Results:** Results (Table) reveal that in HF state, SEPCA2a was significantly decreased, Exchanger was significantly increased while YPYR2 was unchanged in both mRNA and protein levels. However, all three Ca$^{2+}$-handling molecules in both mRNA and protein levels were relatively preserved in the pacing plus PT group.

**Conclusion:** Thus, PT may ameliorate cardiac function during development of HF in part via normalization of expression of Ca$^{2+}$-handling proteins.

**1206-146 Effect of Vasopeptidase Inhibition With Omapatrilat in a Canine Model of Tachycardia-Induced Heart Failure**

I. I. Holzgrafe, Susan D. Arthur, James R. Powell, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, New Jersey, USA

**Background:** Omapatrilat (OMA), a clinically advanced member of a novel class of cardiovascular compounds, the vasopeptidase inhibitors (VPIs), simultaneously inhibits neutral endopeptidase and angiotensin converting enzyme.

**Methods:** The effect of chronic oral therapy with OMA (10 mg/kg bid) and an ACE inhibitor (fosinopril) (FOS) (30 mg/kg bid) alone, or in combination with a diuretic (furosemide, 30 mg/kg bid) were compared in a canine model of pacing-induced cardiomyopathy. Pacing and stimulating electrodes were surgically implanted to produce rapid right ventricular pacing (RVP) at 210 bpm. Following surgical recovery, dogs were randomly assigned to one of 6 treatment protocols (see table). Systemic hemodynamic parameters were measured after 28 days of drug and RVP. Data (mean ± standard error) were compared by one-way ANOVA or Students t-test as appropriate.

**Results:** Results (Table) reveal that in HF state, SERCA2a was significantly downregulated in both mRNA and protein levels. However, all three Ca$^{2+}$-handling molecules in both mRNA and protein levels were relatively preserved in the pacing plus PT group.

**Conclusion:** Thus, PT may ameliorate cardiac function during development of HF in part via normalization of expression of Ca$^{2+}$-handling proteins.

**Table**

<table>
<thead>
<tr>
<th>Group</th>
<th>Wall Stress (g/cm²)</th>
<th>LVEDV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham (n = 6)</td>
<td>16.5 ± 2.0</td>
<td>104.0 ± 5.9</td>
</tr>
<tr>
<td>Furosemide (n = 6)</td>
<td>65.0 ± 4.8</td>
<td>77.3 ± 9.5</td>
</tr>
<tr>
<td>Fosinopril (n = 6)</td>
<td>58.5 ± 11.5</td>
<td>146.1 ± 6.3</td>
</tr>
<tr>
<td>Fosinopril + FOS (n = 6)</td>
<td>41.3 ± 5.3</td>
<td>150.5 ± 6.4</td>
</tr>
<tr>
<td>OMA + Fosinopril (n = 6)</td>
<td>51.7 ± 4.4</td>
<td>158.8 ± 6.4</td>
</tr>
</tbody>
</table>

*p < 0.05 vs Vehicle; **p < 0.05 vs OMA

**Conclusions:** OMA reduced ventricular dilation, resulting in a reduction of diastolic wall stress in a canine model of pacing-induced cardiomyopathy. Beneficial effects were significantly greater than those produced by either an ACE inhibitor or combination ACE inhibitor plus diuretic. OMA may offer a novel therapeutic approach to the prevention and treatment of patients with evolving heart failure compared with conventional therapy.
**1206-147** Gene Expression of C-Type Natriuretic Peptide Is Induced by Heart Failure and Markedly Suppressed by Aging in the Mouse Lung  

**Backgrounds:** The molecular adaptations induced by heart failure (HF) in the lung and the influence of aging on these processes remain poorly defined. C-type natriuretic peptide (CNP) is produced by endothelial cells and causes vasorelaxation through the activation of natriuretic peptide receptor B (NPRB) on smooth muscle cells. CNP also inhibits angiotensin II dependent endothelin 1 gene expression (Uic) and it may thus play a role in modulating pulmonary hemodynamics, especially when vasoconstricting neurohumoral systems are activated. We have used a previously described transgenic (TG) mouse model of HF (resulting from cardiac-specific expression of a mutant myosin heavy chain) to assess whether CNP and NPRB GE in the lung is altered early during the development of HF, and how this process is modulated by aging.

**Methods:** Lungs were obtained from 8 and 12 months old (m.o.) male TG mice (8 and 6 animals respectively) and from age and size matched non-TG littermate controls (CT). At these ages TG mice exhibit severe, progressive left ventricular dilatation and systolic dysfunction, but not yet significant lung and liver congestion. GE was assessed by semiquantitative RT-PCR and β-actin mRNA levels were used as a normalization control (NPRB and CNP mRNA levels).

**Results:** CNP GE was increased in the lungs of 8 m.o. TG mice, when compared to age-matched CT mice (1.5 fold, p < 0.05), but this increase was no longer significant in the 12 m.o. mice. Moreover, CNP GE was significantly lower in the older mice (either TG or CT) when compared to 8 m.o. mice (fold, p < 0.05). NPRB GE was similar in TG and CT mice and it was >2 fold lower in the older mice.

**Conclusion:** CNP GE is induced by HF and suppressed by aging in the mouse lung, NPRB GE, while not altered by HF, is also suppressed by aging. Enhanced CNP expression appears to be a transient pulmonary adaptation to heart failure that is suppressed by aging.

**1206-148** Antioxidant Vitamins Attenuate Cardiac Dysfunction in Tachycardia-Induced Cardiomyopathy  
J. D. Shute, J. Garett, A. Mohan, J. Chang-seng, L. University of Rochester Medical Center, Rochester, New York, USA

**Background:** Increasing evidence suggests that oxidative stress plays an important role in heart failure. Recent studies show that antioxidant vitamins C, E, and β-carotene attenuate neuronal-induced B receptor downregulation and improve cardiac β-adrenergic responsiveness. We speculate that β-carotene may exert beneficial effects in heart failure when oxidative stress is in excess.

**Methods:** Rabbits with rapid ventricular pacing (300 bpm) were randomly assigned to receive vitamin subcutaneous pellets (A: 20 mg, C: 200 mg, E: 200 mg) or placebo for 8 weeks, and compared to control rabbits without pacing (n = 10 in each). We measured: 1) serial LV end-diastolic dimension (DD) and fractional shortening (FS); 2) ECG/angiography; 3) LV isoproterenol response to isoproterenol ([Ca2+]i); and 3) total oxidative stress by measuring the ratio of myocardial reduced to oxidized glutathione (GSH/GSSG).

**Results:** Rapid pacing produced progressive increase of DD and decline of FS. β-Carotene decreased the changes of DD and FS in pacing (Figures). The end of 8 weeks, pacing resulted in a reduced [Ca2+]i in the control group (Control 266 ± 72, Pacing 169 ± 98). An increase in GSSG was also observed as a decrease in GSH/GSSG (32 ± 5 vs 17 ± 5). Vit improved [Ca2+]i in pacing animals to 2304 ± 151 and GSH/GSSG to 71 ± 5 (values are means ± SE, *p < 0.05 vs Control, **p < 0.05 vs Pacing).

**Conclusion:** Myocardial oxidative stress was increased in pacing-induced heart failure. Antioxidant Vit reduced the total oxidative stress and attenuated the systolic dysfunction. LV remodeling and β-adrenergic receptor subsensitivity. The result suggests antioxidant therapy may be beneficial in the treatment of heart failure.

**1206-149** Effects of Candesartan and Enalapril on Cardiomyopathy  
J. Y. Min, J. P. Morgan, A. Meissner, R. Simon, BIDMC-Harvard Medical School, Boston, USA, University of Kiel, Germany

**Background:** The molecular adaptations induced by heart failure are established tool for the treatment of heart failure. However, the cellular mechanism of this beneficial effect remains obscure. The present study investigated the effects of chronic Candesartan and enalapril on contractile function and intracellular Ca2+ homeostasis in failing myocardium from postinfarction rats.

**Methods and Results:** Myocardial infarction was induced by permanent ligation of the left coronary artery. The animals were treated orally with placebo or Candesartan (10 mg/kg/d) or enalapril (10 mg/kg/d) or a combination of both drugs, isotropic force, tachykinetic force and the free intracellular Ca2+ concentration ([Ca2+]i) were determined in papillary muscles (PM) after 6 weeks of chronic treatment. In comparison to the placebo group, PM from the drug-treated groups exhibited a marked improvement of isometric force and a minor increase of systolic [Ca2+]i both at control conditions as well as on firing isometric stimulation. Moreover, the myofilibrillar Ca2+ responsiveness as estimated by the force generation of tetanized preparations was significantly increased in PM from the drug-treated groups.

**Conclusion:** In failing myocardium from postinfarction rats, combined therapy with candesartan and enalapril proved to be the most effective regimen to improve contractile force, systolic Ca2+ handling and myofilibrillar Ca2+ responsiveness.

**1206-150** Increased Aldosterone Synthase and Type I Mineralocorticoid Receptor Expression in Experimental Chronic Heart Failure  

**Background:** The systemic renin-angiotensin-aldosterone system is stimulated following myocardial infarction (MI). While the local, cardiac renin-angiotensin system is involved in left ventricular (LV) remodeling after MI, the role of the recently discovered cardiac steroid system is unclear. We evaluated quantitatively changes of the local steroid system in experimental heart failure after MI.

**Methods:** Three months after coronary ligation or sham-operation (Sham), hemodynamic studies were performed in male Wistar rats. Competitive RT-PCR of right and left ventricular (RV, LV) tissue samples were done.

**Results:** LV end-diastolic pressure (LVEDP) was significantly increased by MI (Sham: 2.8 ± 0.8 mmHg, n = 7; Large MI area 38.8 ± 4.4%). 5.3 ± 0.2 mmHg, n = 7; Extensive MI areas 23.0 ± 2.0%). 13.9 ± 0.4 mmHg, n = 7; p < 0.05 vs Sham). LV mRNA-expression of aldosterone synthase (CYP 11B2), the key enzyme of aldosterone synthesis, was significantly increased about 2.5 fold, while the expression of 11b-hydroxysteroid (CYP 11B1) was decreased by 14%. In addition, LV type 1 mineralocorticoid receptor (MR) expression was increased up to 3.2 ± 0.4 attomol/µg RNA in extensive MI vs Sham-operated rats (1.0 ± 0.3 attomol/µg RNA; p < 0.05). Increase of MR-expression was significantly correlated to MI-induced increase of LVEDP (p = 0.05). In cells transfected with the human MR, isoproterenol-induced increase of intracellular CaM was 7 fold increased vs wild-type cells pointing to a MR-mediated modulation of cellular cationic signaling. LV-expression of the glucocorticoid receptor (GR) was unchanged.

**Conclusion:** Receptors and enzymes of the steroid system are locally expressed and modulated in chronic heart failure after experimental MI probably due to severe myocardial dysfunction. The clinical relevance of these findings is supported by the beneficial effects of MR-blockade in congestive heart failure in addition to ACE-inhibition (RALES-study).
Heart Failure Diagnosis and Disease Management
Wednesday, March 15, 2000, 9:00 a.m.–11:00 a.m.
Anaheim Convention Center, Hall A
Presentation Hour: 10:00 a.m.–11:00 a.m.

Predicting the Absence of Coronary Disease in Patients With Systolic Heart Failure of Unclear Etiology

Background: It is controversial whether all patients with systolic heart failure (CHF) of unclear etiology should undergo coronary angiography in order to identify patients with coronary disease (CAD) who might benefit from revascularization.

Methods: The prevalence of CAD (>50% stenosis in a major vessel) was studied in all patients with a primary diagnosis of CHF of unclear etiology who underwent angiography at an inner city public hospital over 5 years. Patients were categorized into three groups based on the presence of CAD: group 1: 50% known CAD, prior myocardial infarction, or another etiology for CHF (eg, valve disease) were excluded.

Results: Of 124 patients (50% male, age 55 ± 11 yr, ejection fraction 38 ± 10%), 27% had CAD, including 15% with "severe CAD" (left main, 3-vessel, or 2-vessel involving the proximal left anterior descending). Multivariate predictors of the absence of severe CAD in these patients included absence of diabetes (OR 0.25; 95% CI 0.08-0.82; p = 0.02) and >2 other risk factors (OR 0.26; 95% CI 0.09-0.84; p = 0.07); age and absence of Q waves or left bundle branch block (Q/LBBB) on electrocardiogram were borderline significant (both p = 0.06). Use of a retrospectively defined algorithm (performing angio only in patients with diabetes, >2 other risk factors, or Q/LBBB) would have identified 94% of patients with CAD, including 100% with severe CAD, and avoided angiography in 44% of patients without CAD.

Conclusions: Severe CAD is not uncommon in patients with systolic CHF of unclear etiology, suggesting that a strategy of routine angiography may be appropriate. However, if confirmed by further studies, application of a simple algorithm using clinical parameters that are easily determined may eliminate the need for angiography in many patients without significant CAD.

Volume Overload and Co-Morbid Conditions of Hospitalized Heart Failure Patients
Keith Aonson, Pamela Russman, David Frumkin, Todd Koelling, David B. Dyke, Robert J. Cody, University of Michigan, Ann Arbor, Michigan, USA

Background: Heart failure is a common discharge diagnosis, particularly within the elderly population. We evaluated a cohort of patients admitted over a two year period, to identify characteristics contributing to this phenomenon. Methods: Patients admitted to the University of Michigan medical center during 1996 and 1997 were evaluated. Charts were abstracted and data entered for all features relevant to clinical characterization, using standard coding and practice guideline parameters. Only one index admission was entered into the analysis for each patient. Data were scanned and analyzed for demographic features and associated features.

Results: 312 admissions were identified in the specified time period, with an age of 64.5 ± 15 years, and males were 60.1%. 11.5% of all patients were <50 years of age, 45.3% of the total cohort had an age of 64.5 ± 15 years. 40% had diabetes mellitus. 45% of pts had an ischemic etiology, 21% had systolic dysfunction with mixed etiology. 61% had hypertension, 35% had atrial fibrillation, and 29% had renal insufficiency, and active smoking were not exclusion criteria, and where present, or 2-vessel involving the proximal left anterior descending. Multivariate predictors of the absence of severe CAD in these patients included absence of diabetes (OR 0.25; 95% CI 0.08-0.82; p = 0.02) and >2 other risk factors (OR 0.26; 95% CI 0.09-0.84; p = 0.07); age and absence of Q waves or left bundle branch block (Q/LBBB) on electrocardiogram were borderline significant (both p = 0.06). Use of a retrospectively defined algorithm (performing angio only in patients with diabetes, >2 other risk factors, or Q/LBBB) would have identified 94% of patients with CAD, including 100% with severe CAD, and avoided angiography in 44% of patients without CAD.

Conclusions: Severe CAD is not uncommon in patients with systolic CHF of unclear etiology, suggesting that a strategy of routine angiography may be appropriate. However, if confirmed by further studies, application of a simple algorithm using clinical parameters that are easily determined may eliminate the need for angiography in many patients without significant CAD.

Cardiovascular Function and Heart Failure
1207-l 52

1207-l 53

Heart Failure TreatmenrProgram
Health Maintenance Organization Patients in the Absence of Coronary Disease in Heart Failure Patients

Background: Academic heart failure (HF) management programs have been successful at reducing hospitalizations, decreasing hospitalizations, and decreasing mortality in uncomplicated HF patients (pts). However, pts in these programs are often cardiac transplantation candidates and, as such, lack the comorbidities of a general patient population. We sought to evaluate the success of a program where comorbidities such as diabetes mellitus, chronic renal insufficiency, and active smoking were not exclusion criteria, and where social support was not an entry requirement.

Methods: We studied 183 consecutive pts with systolic dysfunction enrolled in our HF treatment program (HFTP) prior to February 15, 1999. Entry criteria included an ejection fraction < 0.40, class III or IV New York Heart Association (NYHA) symptoms, and a creatinine < 3.5 mg/dl. Mean age = 61 ± 13 years. 40% had diabetes mellitus. 45% of pts had an ischemic etiology. Diuretics and angiotensin converting enzyme inhibitors (ACEI) were titrated to optimal dosing to achieve clinical compensation (ClinComp), defined as achieving a stable weight for at least 2 weeks with best functional class possible. Sota trocters were then up-titrated in the usual fashion.

Results: Total hospital days were decreased from 641 for the 6 months prior to entry into the HFTP to 292 days (p < 0.05) for the 6 months after entry. Actuarial survival at 12 month was 91%. Mean follow up was 13.3 ± 5.3 months.

NYHA class ACEI (mg) ClinComp (%)
Initial 3.3 ± 0.4 20 ± 16 29
Min/Max 2.4 ± 0.7 p < 0.001 29 ± 15, p < 0.01 77, p < 0.001

Conclusion: In a diverse HMO population with a high proportion of pts with comorbidities, especially diabetes mellitus, a HF management program can achieve significant improvement in NYHA class and clinical compensation with good survival and substantial cost savings from a greater than 50% decrease in hospital days.

1207-l 54

Outcomes Improve and Hospitalizations Fall for Health Maintenance Organization Patients in Heart Failure Treatment Program
Catherine Chelminsky-Fallick, John S. Golden, Donna J. Matecki, E. Kirk Huang, Cecilia A. Gnecey, Colleen M. Hooley, Sharon R. Jocophen, Mary C. Langford, Susan J. Morikawa, Carol A. Offutt, Patricia A.G. Powers, Shonida Spell-Hampton, Suzanne J. Wingate, Cardiology, Kaiser Permanente Mid-Atlantic States, Rockville, Maryland, USA

Background: Hospitalized heart failure (HF) patients at high risk for death and/or hospitalization: NYHA Class (p < 0.001), ischemic heart disease (p = 0.0031), diabetes mellitus (0.0035), atrial fibrillation (0.0035), S-urea acid (p = 0.0436) and relative lymphocyte concentration (p = 0.0462). In addition, the relative hazard rate (i.e. relative hazard rate, RHR) of losartan/captopril decreased with an increase in risk score, (0.62 < RHR < 0.59, when 0.17 < R < 10.0).

Conclusions: The independent risk factors for morbidity and mortality identified in this study are consistent with those previously reported: a morbidity/mortality risk score can be used to identify potential high risk patients. Furthermore, in this study, the relative hazard rate shows that losartan has a greater effect in high-risk patients vs. captopril.
Introduction: Heart failure presents an increasing clinical burden for both patients and physicians. Changes in clinical practice frequently lag behind advances in treatment described in large clinical trials. The Canadian CHF Clinics Network has established in 11 initial centres across Canada to improve the current management of chronic heart failure (CHF), to implement new proven therapies in a timely manner, and to collaborate in innovative research approaches to optimize patient management. By consensus, a manual of CHF management for physicians, nurses, and patients, a national computerized database, and a strategy of education to enhance CHF treatment in the community have been developed.

Results: Selected mean characteristics of the 573 patients entered into the database over the first 6 months are: age 60 years; male 73%; ischemic 27%; NYHA Class I 19%, II 21.9%, III 35.6%, IV 12.4%; LVEF 22%, LVEF > 45% 4.7%. Minnesota HF score 44. history of hypertension 25%; dyslipidemia 27%; diabetes 23%; current smoker 7%; renal dysfunction 10%; atrial fibrillation 18%. Treatment profiles for drug use were: ACE-I 83%; AT1 blocker 29%; NYHA Class I 7.9%, II 29.1%, III 35.6%, IV 12.4%; LVEF 22%, LVEF > 45% 4.7%; Minnesota HF score 44; history of hypertension 25%; dyslipidemia 27%; diabetes 23%; current smoker 7%; renal dysfunction 10%; atrial fibrillation 18%. Treatment profiles for drug use were: ACE-I 83%; AT1 blocker 29%; beta blockers 48%; furosemide 88%; digoxin 60%; long acting nitrates 35%; statin 37%; warfarin 37%; amlodipine 13%; amiodarone 15%; carvedilol 29%.

Methods: Patients with either ejection fraction < 20%, recent hospitalization for CHF, or New York Heart Association (NYHA) class III and IV CHF were enrolled in the Duke Heart Failure Program between 7/28/97 and 7/14/99 (n = 95). Data on age, ejection fraction, electrocardiogram, referring physician, angiotensin converting enzyme inhibitor (ACEI) and beta-blocker (BB) use, target ACEI and BB dose, hospitalizations, and clinic visits were collected from clinic notes and administrative databases. Analyses were performed using Wilcoxon rank sum test to compare continuous variables and chi-square test to compare categorical variables.

Results: The mean age was 82 ± 14 years; 88% were female; 47% lived greater than 30 miles from the medical center; 58% were NYHA class III and IV; and the median ejection fraction was 25%. The median time in the program was 4.9 months. Although ACEI use did not increase significantly, ACEI dose did (74% vs 97% of target dose, p = 0.02). BB use and dose significantly increased (52% vs 76% on 88 mg, 7.2% vs 40% of target dose, p < 0.001 for both). Hospitalization rate and ALOS significantly decreased (1.8 hosp/pt year vs 1.21 hosp/pt/year, p = 0.01; 7.67 vs 6.07 days, p = 0.01). Total clinical visits and cardiology clinic visits, including heart failure clinic visits, significantly increased (7.8 vs 12.9 visits/pt year, p = 0.001 for total; 1.5 vs 7.7, p = 0.001 for cardiology). Outpatient costs increased 27% and inpatient costs decreased 38% (p = NS for both). Cost per discharge decreased 32% (p < 0.001). Total cost decreased 37% (p = 0.06). The number of patients who reported utilization of outpatient office visits, hospitalization and emergency room visits decreased after 4, 8 and 12 weeks of service use to the 4 week period prior to service use. The percentage of patients who reported weighting daily increased from 17% to 25% after 4-8 weeks (p = 0.02). Heart failure costs for the intervention group decreased 41% during 6 months of service use compared to a 3.2% increase observed in the control group.

Conclusion: A managed care support service can enhance quality of life and reduce hospitalizations in HF patients. These reductions are associated with significant cost savings.

Background: The diagnostic evaluation of congestive heart failure (CHF) has been identified as a means of improving quality of care, but little is known about their impact on cost. We hypothesized that a heart failure program would result in improved quality of care at reduced cost.

Methods: Patients with either ejection fraction < 20%, recent hospitalization for CHF, or New York Heart Association (NYHA) class III and IV CHF were enrolled in the Duke Heart Failure Program between 7/28/97 and 7/14/99 (n = 95). Data on age, ejection fraction, electrocardiogram, referring physician, angiotensin converting enzyme inhibitor (ACEI) and beta-blocker (BB) use, target ACEI and BB dose, hospitalizations, and clinic visits were collected from clinic notes and administrative databases. Analyses were performed using Wilcoxon rank sum test to compare continuous variables and chi-square test to compare categorical variables.

Results: The mean age was 82 ± 14 years; 88% were female; 47% lived greater than 30 miles from the medical center; 58% were NYHA class III and IV; and the median ejection fraction was 25%. The median time in the program was 4.9 months. Although ACEI use did not increase significantly, ACEI dose did (74% vs 97% of target dose, p = 0.02). BB use and dose significantly increased (52% vs 76% on 88 mg, 7.2% vs 40% of target dose, p < 0.001 for both). Hospitalization rate and ALOS significantly decreased (1.8 hosp/pt year vs 1.21 hosp/pt/year, p = 0.01; 7.67 vs 6.07 days, p = 0.01). Total clinical visits and cardiology clinic visits, including heart failure clinic visits, significantly increased (7.8 vs 12.9 visits/pt year, p = 0.001 for total; 1.5 vs 7.7, p = 0.001 for cardiology). Outpatient costs increased 27% and inpatient costs decreased 38% (p = NS for both). Cost per discharge decreased 32% (p < 0.001). Total cost decreased 37% (p = 0.06). The number of patients who reported utilization of outpatient office visits, hospitalization and emergency room visits decreased after 4, 8 and 12 weeks of service use to the 4 week period prior to service use. The percentage of patients who reported weighting daily increased from 17% to 25% after 4-8 weeks (p = 0.02). Heart failure costs for the intervention group decreased 41% during 6 months of service use compared to a 3.2% increase observed in the control group.

Conclusion: A managed care support service can enhance quality of life and reduce hospitalizations in HF patients. These reductions are associated with significant cost savings.

Background: The 1994 Agency for Health Care Policy and Research consensus guidelines for the diagnostic evaluation of congestive heart failure (CHF) recommend a baseline evaluation of ventricular systolic function and a laboratory and clinical search for reversible causes of CHF. There are no population-based studies to evaluate current practice patterns and their outcomes.

Methods: The REACH study is a prospective cohort study of 26,442 CHF patients within the Henry Ford Health System (HFHS) in Detroit, Michigan. Claims data from all diagnostic procedures were available from 1995–1998 in 3353 patients with CHF diagnosed within one year, who were members of the HFHS health maintenance organization. These individuals are homogeneous with respect to access to care and cardiac procedures.

Results: Rates for diagnostic tests were as follows: chest x-ray 88%, EKG 99%, echocardiogram 71%, radionuclide ventriculogram 7%, coronary catheterization 52%, stress testing 30%, biochemical profile 90%, complete blood count 88%, urinalysis 74%, and thyroid stimulating hormone 46%. The mortality rates were 5% and 6% in the groups with some form of ischemic evaluation (stress test or cath) versus none, p = 0.15. Likewise there were no differences in mortality (6% vs 5%) in those with and without measures of ventricular function (echo or MUGA), p = 0.56.

Conclusion: Unlike consensus guidelines for treatment, guidelines with respect to the diagnostic evaluation of congestive heart failure have not been uniformly implemented and may not have an impact on short term mortality given the targeted use of tests by clinicians based
Quality of Life Measurements Predict Mortality and Hospitalization in Patients With Advanced Heart Failure. Insights From The EPICAL Study

François Alta, Serge Bilancón, Yves Jullière, Paul-Michel Mertes, Jean-Pierre Villemot, François Guillermu, Fabrice Zaremba. The EPICAL Investigators: Epidemiology and Cardiology. Clinical Investigation Center, INSERM-CHU, University Henri Poincaré, Nancy, France

Background: Survival and quality of life (QOL) are poor in patients with congestive heart failure (CHF). Coronary angiography was performed in 108 patients registered in the EPICAL program (JACC 1999;33). This program identified patients with severe CHF defined by a hospitalization for a NYHA grade III/IV dyspnea, edema or hypotension, and LVEF < 30%. Questionnaires were previously translated and transculturally validated in French. Scores ranged from 0 (poorest QOL) to 100 (best QOL). QOL measures were performed one month after hospital discharge. General, physical, mental and social dimensions, adjusted for other prognostic variables were tested in a multivariate Cox model.

Results: QOL was poor (10HF global score: $64 \pm 7$; MI HF global score: $66 \pm 8$). One year survival was $78\%$ and one year hospital-free-survival $38\%$. With both questionnaires and on univariate analysis, general and physical dimensions were significantly associated with survival while general, physical, and social dimensions were significantly associated with hospital-free-survival. Only in the MIHF questionnaire, this relation remained significant for hospital free survival after adjustment for other prognostic factors (serum sodium, history of renal failure, number of prior hospitalizations and duration of the cause of death). RR associated with 10 points decrements in the score of global, physical and social dimensions in the MIHF questionnaire were respectively 1.17 [1.01-1.36], 1.16 [1.03-1.30] and 1.13 [1.02-1.24].

Conclusion: QOL assessment is a predictor of mortality and is an independent predictor of hospitalization free survival in patients with advanced heart failure. QOL assessment with disease specific questionnaire may provide additional information for routine clinical management and therapeutic decision as well as for risk stratification in clinical trials.

Poster

Heart Transplant: Graft Function

Wednesday, March 15, 2000, 9:00 a.m.-11:00 a.m.
Anaheim Convention Center, Hall A
Presentation Hour: 10:00 a.m.-11:00 a.m.

Absence of L-Arginine Effect on the Coronary Hypersensitivity to Serotonin in Cardiac Transplant Recipients


Klinikum Großhadern, University of Munich, Munich, Germany

Background: Coronary hypersensitivity to serotonin (5HT) promotes platelet aggregation and therefore, the progression of the atherosclerotic process. This abnormality occurs in the early stages of coronary atherosclerosis when the responses to bradykinin (Bk) are still preserved.

Methods: We investigated epicardial (QCA) and microvascular (isDoppler) vasodilation in response to 5HT in 15 mg/kg/min and 5 mg/kg/min ic in 22 heart transplant recipients (HTR), a population prone to endothelial dysfunction and morphological coronary abnormalities, 31 ± 8 years after transplantation. FMD was evaluated as acetylcholine response (ACH 150 mcg/5 min before and after ic injection.

Results: Q increased proximal (6 ± 8\%, p < 0.05) and distal (14 ± 10\%, p = 0.01) epicardial coronary diameter and increased blood flow (coronary flow reserve, CFR) 2.2 ± 0.5, p < 0.01). CFR to Q correlated inversely to LIMNA-taxed basal NO-mediated blood flow (r = 0.50, p = 0.01) and was independent of epicardial intimal thickening (IVUS) or endothelial dysfunction. Epicardial endothelial dysfunction (i.e. >10% diameter decrease in response to ACH) was less prevalent after Q (26% decrease of diameter vs. 48% decrease of diameter after iv injection, $p < 0.05$), whereas microvascular endothelial dysfunction (i.e. CFR to ACH < 2.5) remained unchanged.

Conclusion: L-arginine increases epicardial vasodilation and the microcirculation in HTR; independent of functional and morphological alterations, Epicardial endothelial dysfunction improves acutely after Q. These beneficial effects of Q on coronary vasomotion and endothelial function probably may lead to a lower incidence of functional and morphological manifestations of cardiac allograft vasculopathy during long-term treatment with this drug.
Serial Assessment of Coronary Flow Reserve in Pediatric Cardiac Transplant Recipients

Shinichiro Nuncda, Chieko Fuji, Norihito Hotta, Makoto Shinganwa, Yuuki Kufo, Kuniuki Ohtsuka, Shin-Ichiro Okawa, Department of Medicine, Tokyo Women's Medical University, Daini Hospital, Tokyo, Japan

Background: Intracoronary ultrasound (ICUS) provides an information of epicardial allograft vasculopathy (AV) in transplant (Tx) recipients (Rs). However, it is difficult and risky to do it frequently in pediatric Tx Rs, and to assess the AV which appears also in intramyocardial coronary vessels.

Methods: The subjects consisted of 6 pediatric Rs (5 months to 11 years) who had been transplanted for at least 3 yrs postTx. The longest fol- low-up period among 6 pediatric Rs was 9 yrs. After injection of isosorbide dinitrate, phasic coronary artery velocity was analyzed in the proximal segment of the angiographic normal intimal and intramyocardial coronary artery using a 0.014-in, 15-MHz Doppler guide wire (DGW). CFR was obtained from the reduction of the time-averaged peak velocity. We also studied clinical risk factors which may contribute to AV.

Results: 2 of 6 Rs showed significant decrease of CFR during the follow-up periods. Of these 2 Rs showed the decrease of CFR from 2.9 at 6 yrs postTx to 1.4, which was obtained a few months before his sudden death at 7 yrs postTx. His coronary angiogram before his death showed the progression of irregularity, however, only at the distal portions. The another patient showed decrease of deceleration time from 150 to 100 msec in his echocardiogram in 4 years post Tx. His coronary angiogram before his death showed the progression of irregularity, however, only at the distal portions. The other patient showed decrease of deceleration time from 150 to 100 msec in his echocardiogram in 4 years postTx. His coronary angiogram before his death showed the progression of irregularity, however, only at the distal portions. The remaining 4 Rs showed no significant decrease of CFR (≤0.5 CFR, 0.1-0.3) during the follow-up periods. Among possible risk factors, suboptimal immunosuppression and renal failure was associated with the progression of AV.

Conclusion: Serial assessment of AV including intramyocardial small vessels can be safely done by using DGW in pediatric Rs and it is possible to modulate postTx care before the manifestation of diastolic or systolic dysfunction.

Impact of Remodeling on Coronary Lumen Loss in Transplant Vasculopathy: A Serial Intravascular Ultrasound Study

Khaled M. Ziadak, Samir P. Kapadia, Marlene Gomma, Falah E. Erteka, Timothy D. Crowe, Gustavo Rincon, Steven E. Nissen, E. Murat Tuzcu. The Cleveland Clinic Foundation, Cleveland, OH, USA

Background: In atherosclerotic disease, arterial remodeling or change in external elastic membrane (EEM) size affects the degree of luminal stenosis. However, the impact of remodeling on lumen size in early cardiac allograft vasculopathy remains undefined.

Methods: Intravascular ultrasound was performed in 127 patients at <8 weeks and 1 year after transplantation. Aortic lumen area (LA), external elastic membrane (EEM) area, internal area (IA = EEM area - LA) and internal thickness (ITmax) were measured. Vasculopathy lesions were sites that contained no disease at baseline and ITmax ≥ 0.8 mm at 1 year.

Results: Vasculopathy lesions identified in 14% (13%) of 67 coronary sites at baseline and 14% (13%) of 67 coronary sites at 1 year follow-up. LA decreased from 15.0 ± 5.7 to 10.2 ± 5.4 mm² and IA increased from 1.9 ± 1.4 to 5.5 ± 2.0 mm² (p < 0.0001 for both). EEM area increased from 17.7 ± 6.1 to 18.8 ± 6.0 (p < 0.0005), although there was EEM area loss at 55% (38%) sites. By stepwise and univariate linear regression, IA and ITmax changes influenced LA change, but the change in EEM area alone explained 70% of the change in LA (figure).

Conclusions: Despite very rapid intimal proliferation, arterial remodeling is the major determinant of the degree of lumen loss in allograft vasculopathy in the first year after transplantation.
**909 Newer Agents for Heart Failure**

Wednesday, March 15, 2000, 10:30 a.m.–Noon
Anaheim Convention Center, Room 304A

### 909-1 Beneficial Effects of Vasopeptidase Inhibition on Mortality and Morbidity in Heart Failure: Evidnce From the Omapatrilat Heart Failure Program

*John R. Knetls, Jean L. Rouleau, Mari A. Pfeiffer, Michel F. Rouxet, Hamid Ikram, Michel Komajda, Chunlin Qian, Alan J. Block, James H. Naylor, David P. Synhorst, Hubert Poulleur.* For the Omapatrilat Heart Failure Investigators (UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ, USA)

**Background:** The vasopeptidase inhibitor, omapatrilat (OMA), inhibits ACE (Ki = 6.0 nM) and neutral endopeptidase (EC 3.4.24.11; Ki = 6.0 nM), which degrades vasoactive peptides including bradykinin, the natriuretic peptides and adrenomedullin.

**Methods:** To assess its long-term safety in heart failure (HF), a total of 1242 patients (NYHA II, 63%; III, 35%; IV, 1%; EF, 28%) were randomized in two double-blind isotonic (LIS) controlled trials; a 52 week trial (OMA, n = 540; dose = 20 mg; LIS, n = 542; dose = 20 mg) and a 24 week trial (OMA, n = 289; dose = 40 mg; LIS, n = 284; dose = 20 mg).

**Results:** In each trial, OMA improved the combined endpoint of death or hospitalization for worsening HF (RR: 0.78, 95% CI: 0.56, 1.11 with 20 mg; RR: 0.53, 95% CI: 0.27, 1.02 with 40 mg). In the pooled analysis, there was a statistically significant reduction with OMA (RR: 0.72, 95% CI: 0.53, 0.97; figure).

Both drugs were well tolerated. The overall incidence of cardiovascular serious adverse events (AE), AE of renal dysfunction, and marked elevations in creatinine were lower with OMA than with LIS. Hypotension was more common with OMA (11.0% vs. 6.5%) but syncope occurred more often with LIS (5.1% vs. 1.4%). There was one case of angioedema with LIS and none with OMA.

**Conclusions:** In these studies, vasopeptidase inhibition with OMA appeared superior to ACE-I in preventing death and worsening HF. A definitive trial of 6240 patients, OVERTURE, is enrolling to compare omapatrilat with a 40 mg dose of OMA.

### 909-2 Subcutaneous BNP Administration in Symptomatic Human Heart Failure: A Novel Therapeutic Strategy for Congestive Heart Failure

*Hong H. Chen, Lynda J. Nordstrom, Margaret M. Reisfield, John C. Burnett, Jr., Mayo Clinic, Rochester, MN, USA*

**Background:** Brain natriuretic peptide (BNP) is a cardiac hormone with vasodilating, natriuretic, renin-angiotensin-aldosterone (RAAS) inhibiting and lusitropic properties. We have previously demonstrated downregulatory effects of intravenous immunglobulin (IVIG) on various inflammatory and immunomodulatory parameters with relevance for CHF. We therefore examined the effect of long-term treatment with IVIG on functional capacity and cardiac performance in patients with CHF.

**Methods:** 41 patients (mean age 60 ± 9 years), with chronic symptomatic CHF and left ventricular ejection fraction (LV-EF < 40%), 23 with coronary artery disease (CAD) and 18 with diastolic dilated cardiomyopathy (DDCM), already optimally treated (93% ACE-inhibitors, 76% β-blocker) were randomized between IVIG (0.4 mg/kg i.v. as a daily infusion for 6 days and thereafter as one infusion each month) and placebo in a double-blind trial lasting for 6 months. Efficiency parameters were examined at baseline and end of study.

**Results:** (i) LV-EF increased from 20 ± 2 to 31 ± 3% during IVIG (p < 0.01) while remaining unchanged in the placebo group (28 ± 2 to 29 ± 2%, ns). (ii) Both the beneficial effect on LV-EF in the IVIG group was most marked in those with CAD and in those with LV-EF > 15% at baseline. (iii) IVIG also increased the peak VO2 (p = 0.06) and significantly decreased pulmonary capillary wedge pressure (p < 0.03), while no such effects were seen in the placebo group. (iv) Both in the placebo group (p < 0.05) and particularly in the IVIG group (p = 0.005), there was a significant improvement in clinical performance as evaluated by NYHA classification. (v) In the IVIG group there was a ~35% reduction in plasma pro-ANF levels (p < 0.003), while no change was seen in the placebo group.

**Conclusions:** In patients with moderate to severe CHF on optimal cardiovascular treatment regimens, immunomodulating therapy with IVIG resulted in increased functional capacity, cardiac performance and hemodynamic variables. Our findings underscore a potential for immunomodulating therapy in such patients, and larger studies examining the effect of IVIG or other immunomodulating agents in CHF patients including the effect on mortality, are warranted.

### 909-3 Effect of Immunomodulating Therapy With Intravenous Immunglobulin in Chronic Heart Failure

*Lays Gullesstad, Halvdan Aass, Jan Fjeld, Halvdan Ihlen, Svein Simonsen, John Kjekshus, Sigurd Nitter Hauge, Thor Ueland, Stig S. Freiand, Pål Austvoll, Tlawholesiapetso, Oslo, Norway*

**Background:** Immunologic and inflammatory responses appear to play a pathogenic role in the development of CHF. We and others have previously demonstrated downregulatory effects of intravenous immunoglobulin (IVIG) on various inflammatory and immunomodulatory parameters with relevance for CHF. We therefore examined the effect of long-term treatment with IVIG on functional capacity and cardiac performance in patients with CHF.

**Methods:** 41 patients (mean age 60 ± 9 years) with chronic symptomatic CHF and left ventricular ejection fraction (LV-EF < 40%), 23 with coronary artery disease (CAD) and 18 with diastolic dilated cardiomyopathy (DDCM), already optimally treated (93% ACE-inhibitors, 76% β-blocker) were randomized between IVIG (0.4 mg/kg i.v. as a daily infusion for 6 days and thereafter as one infusion each month) and placebo in a double-blind trial lasting for 6 months. Efficiency parameters were examined at baseline and end of study.

**Results:** (i) LV-EF increased from 20 ± 2 to 31 ± 3% during IVIG (p < 0.01) while remaining unchanged in the placebo group (28 ± 2 to 29 ± 2%, ns). (ii) Both the beneficial effect on LV-EF in the IVIG group was most marked in those with CAD and in those with LV-EF > 15% at baseline. (iii) IVIG also increased the peak VO2 (p = 0.06) and significantly decreased pulmonary capillary wedge pressure (p < 0.03), while no such effects were seen in the placebo group. (iv) Both in the placebo group (p < 0.05) and particularly in the IVIG group (p = 0.005), there was a significant improvement in clinical performance as evaluated by NYHA classification. (v) In the IVIG group there was a ~35% reduction in plasma pro-ANF levels (p < 0.003), while no change was seen in the placebo group.

**Conclusions:** In patients with moderate to severe CHF on optimal cardiovascular treatment regimens, immunomodulating therapy with IVIG resulted in increased functional capacity, cardiac performance and hemodynamic variables. Our findings underscore a potential for immunomodulating therapy in such patients, and larger studies examining the effect of IVIG or other immunomodulating agents in CHF patients including the effect on mortality, are warranted.

### 909-4 Safety and Efficacy of ENBREL® (Etanercept) in the Treatment of Chronic Heart Failure

*Bykem Rozkurt, Guillermo Toro-Amine, Oxitem Z. Soran, Arthur M. Feldman, James Whitmore, Marshelle Warren, Douglas L. Mann.* Baylor College of Medicine, Houston, TX, University of Pittsburgh, Pittsburgh, PA; Immunex Corporation, Seattle, WA; Baylor College of Medicine, Houston, TX, USA

**Background:** Previous studies in heart failure patients have shown that inhibition of TNF by etanercept in patients with heart failure improves clinical endpoints during 3 months of continuous treatment. This follow-up study investigates the safety of etanercept with treatment up to 6 additional months, and describes continuing efficacy and lack of a rebound effect in patients who were withdrawn from etanercept therapy.

**Methods:** Forty-seven patients with NYHA class III–IV heart failure were studied for 3 months in a randomized, double-blind, placebo-controlled trial. Four patients discontinue from the double-blind portion of this trial. Following completion of the 3-month blinded trial, 12 of the patients started on a 6 month, open-label extension arm of the trial. The remaining 31 patients (placebo = 10, etanercept = 21) were discontinued from study drug and followed for an additional 3 months to evaluate loss of effect over time. These patients were then offered open-label treatment in a separate protocol.

**Results:** For patients who were continued on the open-label extension arm of the trial, there was (1) no increase in the frequency of adverse events, (2) evidence of a sustained improvement in NYHA class. For patients who were discontinued from study drug, there was (1) no increase in serious adverse events following drug discontinuation, suggesting that there was no rebound effect and (2) the incremental increase in LV EF following 3 months of treatment with 12 mg/kg (p = 0.02) returned to baseline 3 months after
discontinuation of etanercept. The reduction in LV end systolic volume at 3 months of treatment with 12 mg/m² persisted at 1 month after discontinuation of etanercept (p = 0.04). Ten of the etanercept-treated patients with an improvement in NYHA class from baseline, discontinued etanercept after 3 months of treatment. Five (50%) of those patients experienced a return to baseline 30 days after discontinuation of etanercept, consistent with loss of TNF antagonism.

Conclusions. Sustained treatment with etanercept for 8 months appears to be safe and well tolerated in patients with advanced heart failure. Discontinuation of etanercept is associated with a return to baseline in clinical status consistent with a drug effect. No acute rebound was seen. Some left ventricular structural changes persisted off drug for 1 to 3 months, suggesting that the beneficial effects of etanercept on LV remodeling may be sustained.

11:30 a.m.

Acute Hemodynamic and Neurohumoral Effects of Selective ETA Receptor Blockade in Patients With Congestive Heart Failure

Georg Noll, Veselin Mitrovic1, Lukas E. Spieker, Richard Pacher2, Matthias Schulze3, Christoph Schalcher, Wolfgang Kiowski, Thomas P. Lüchter, On behalf of the ET 003 investigators; Cardiologie: University Hopital, Zürich, Switzerland; 1Kochhoff Clinic, Bad Nauheim; 3Heinz-und Kreislaufforschungszentrum, Cardiologie, Dresden, Germany; 2Allgemeines Krankenhaus, Vienna, Austria

Background: Nonselective ETA/B receptor antagonists improve hemodynamics in patients with CHF. Since ET receptors mediate the release of nitric oxide and the clearance of ET-1, selective ETA antagonists are of special interest. The aim of this study was to investigate the hemodynamic effects of the selective ETA receptor antagonist LU135252 in patients with congestive heart failure (CHF).

Methods: The hemodynamic effects of a single oral dose of the selective ETA receptor antagonist LU135252 (1, 10, 30, 100, or 200 mg) were investigated in a multicenter study involving 95 patients with CHF (NYHA II–III) with an ejection fraction ≤35%.

Results: Lung and left atrial pressure (PWP, mm Hg) measured simultaneously correlated with pulmonary vascular resistance, pulmonary capillary wedge pressure (PCWP, mm Hg), right atrial pressure (RAP, mm Hg), and systemic vascular resistance (SVR, dynes sec cm⁻⁵), respectively, while plasma catecholamines remained constant. LU135252 dose-dependently increased Cl and decreased pulmonary vascular resistance (P < 0.05). There was a trend for more pts receiving BMS (28%) to improve by 1 NYHA Class than in the placebo group (8%).

Conclusion: The ETA selective antagonist BMS-193884 produces a favorable hemodynamic response and is well tolerated in pts with HF.

903-B

Improved Hemodynamics With the ETA Selective Receptor Antagonist BMS-193884 in Patients With Heart Failure

William Smith, Bruce Iteld, Thierry Luepfel, Igrathius Thomas, David Delcman, Susan P. Williams, Daniel Reynor, Mel Blumenthal, New Orleans Center Clinical Research, New Orleans, LA; Bristol-Myers Squibb, Princeton, NJ, USA

Background: Endothelin (ET) antagonists may contribute to the management of heart failure (HF) patients (pts). We evaluated the acute hemodynamic effects of BMS-193884 (BMS), an orally administered ETA receptor antagonist

Methods: 116 pts with NYHA Class II–IV HF, LVEF ≤35%, pulmonary capillary wedge pressure (PCWP) ≥16 mmHg, and cardiac index (CI) <2.7 L/min/m² were randomized to double blind treatment with BMS (5 to 200 mg; n = 75) or placebo (PBO; n = 41). Hemodynamics, which were similar at baseline among treatment groups (overall PCWP = 23.3 mmHg and CI = 2.1 L/min/m²), were monitored for 1 hour. Pts were then treated for 4 weeks as outpatients.

Results: BMS was well tolerated, with adverse events evenly divided between pts receiving BMS and placebo. No clinically significant increases in LFTs were noted. The table shows major hemodynamic indices for the treatment groups as adjusted mean changes from baseline 4 hours after dosing.

Conclusion: BMS-193884 improves hemodynamics in a dose-dependent manner without activation of other neurohumoral systems and is well tolerated over a wide dose range.